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Pathological Findings in Nine Children with "Primary" Pulmonary Hypertension. MORGAN BERTHRONG AND TERENCE H. COCHRAN 69

The Clinical and Pathologic Aspects of Premature Perinatal Death. GEORGE W. ANDERSON AND ROBERT E. L. NESBITT, JR. 113

Musical Murmurs. VICTOR A. MCKUSICK, GENEVIEVE E. MURRAY, ROBERT G. PEELER AND GEORGE N. WEBB 136

Abstracts of Papers Presented Before the Meeting of The Johns Hopkins Medical Society in Association with the Alpha Omega Alpha Fraternity 177

Book Reviews 183

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PATHOLOGICAL FINDINGS IN NINE CHILDREN WITH "PRIMARY" PULMONARY HYPERTENSION

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Advances in cardiac surgery and in cardiac catheterization techniques have led to many physiological studies of pulmonary hypertension which occurs in patients with acquired and congenital heart disease, and in cases of parenchymal diseases of the lungs. Investigation of the structural changes in the pulmonary vascular bed of such patients have often demonstrated prominent alterations in the vessels. The cause-or-effect relationship of the vascular lesions to the pulmonary hypertension, however, has often remained obscure in spite of the fact that at autopsy examination the morphological changes in the vessels may have been thought sufficiently widespread and severe to have produced a mechanical obstruction to blood flow and to have provided a reasonable explanation for the clinically demonstrated hypertension.

Rarely, a patient has been studied who had no evidence of pulmonary parenchymatous disease nor indication of primary heart disease of any type, yet who had severe pulmonary hypertension and eventual right-sided cardiac failure. The great majority of these patients have been adults. Histological study of the lungs from such patients has usually shown lesions of the small pulmonary arteries such as arteriosclerosis (1), thromboses (2, 3), or acute or healing arteritis (4, 5). Thrombi which obstructed the major pulmonary arteries have also been observed (6). It is the purpose of this report to describe the morphology of the pulmonary vascular abnormalities found in nine children with pulmonary hypertension who were autopsied in the Department of Pathology of The Johns Hopkins Hospital.

CASE REPORTS

Case 1. S. C. (J.H.H. #11618) was a three-year-old, white female who was admitted for severe muscular weakness. She had been seen three or four months previously for cyanosis and dyspnea when a diagnosis of "congenital heart disease" had been made. One month before admission, she had been in another hospital with hemiplegia. A diagnosis of acute endocarditis with cerebral emboli was considered. On her final admission the temperature was 100°F., the pulse was 128 per minute and the respirations were 32 per minute. She was dyspneic and cyanotic, and showed marked muscular weakness. The heart was enlarged

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to the left and a systolic murmur was audible in the third left interspace. A diastolic thrill was felt in the same area. The lungs were clear. The right arm was flexed and the right leg weak. Cyanosis increased and a rise of temperature to 102°F. occurred. Death followed on the fifth hospital day, in deep cyanosis and with severe dyspnea.

The *autopsy*, (#4854—Dr. Burrows), revealed a well developed and well nourished, cyanotic child having a fine papular skin eruption. There was no edema or transudate. The enlargement of the heart, which weighed 120 grams (normal 60 grams), was the result of right ventricular hypertrophy and dilatation. There apparently was a patent foramen ovale although measurements were not given and the record is not entirely clear. The pulmonary artery was dilated. No other gross changes were described.

Microscopic study showed flat intimal plaques in the large elastic pulmonary arteries with an occasional group of subendothelial foam cells. Medium-sized muscular pulmonary arteries were normal though large in comparison to their adjacent bronchi. Terminal arteries, which lay adjacent to the respiratory bronchioles and alveolar ducts, were larger than normal and showed a slightly thickened media. Intimal fibrous plaques occasionally projected into the lumina, considerably narrowing the vessel. Most of such arteries, however, were not stenotic. One recanalized thrombus was seen. The arterioles in the walls of the atria and alveoli were often normal, extremely thin-walled vessels. Others in this location, however, showed markedly thickened walls and narrowed lumina (Figs. 5–8). The thick walls appeared to be the result of muscular hyperplasia and hypertrophy located between the internal and external elastic lamellae. Hyalinization of the entire wall was sometimes seen. Intimal plaques were also found in these peripheral pulmonary arterioles but no definite thrombi were found. Small bronchial arteries occasionally revealed marked intimal fibrosis severely encroaching upon the lumina of the vessel. No arteritis was found anywhere. The pulmonary parenchyma was normal. The right ventricular myocardium showed marked hypertrophy of the muscle fibers.

This case was first indexed in 1916 as "idiopathic" right ventricular enlargement but after encountering Case #2 of this report, Dr. Walter Dandy, Jr., (then a third year medical student) located this case in the files and demonstrated the pulmonary arteriolar disease.

Case 2. B. C. (J.H.H. #392105) was a three and one half year old, white girl who was admitted for attacks of dyspnea and cyanosis. Well until one year previously, she then developed hoarseness. Later, attacks of dyspnea associated with apprehension occurred which were aggravated by exertion or cold. Cyanosis appeared with these attacks. Weight loss occurred. On physical examination she was seen to be a thin, small child with a precordial bulge, an enlarged heart and a high-pitched ringing pulmonic sound which was split. The blood pressure was 102/52. A soft systolic murmur was heard. The red blood cell count was 4.85 million with a hematocrit of 39. Fluoroscopy showed a full pulmonic conus with pulsations in the lung fields. Bronchoscopy revealed an extrinsic pressure defect of the trachea. She was operated upon and a large pulsating pulmonary artery was wrapped with cellophane (1946). On return to the ward, she had a sudden convulsion and died.

The *autopsy*, (#20039—Mr. Walter Dandy and Dr. John Buckley), showed a well developed child with a left hemothorax, a right pneumothorax, and a pneumopericardium. The heart weighed 80 grams (normal, 66 grams). The enlargement was obviously the result of right ventricular hypertrophy. All valves were normal save for a bicuspid but competent aortic valve. The tricuspid valve measured 6.5 cm. in circumference; the pulmonary 5.0 cm.; the mitral 3.5 cm.; and the aortic 2.75 cm. A slight coarctation of the aorta was present

with the aortic circumference falling from 3.5 cm. in the ascending portion to 2.0 cm. at the site of the obliterated ductus and increasing to 3.0 cm. in the descending thoracic portion. The foramen ovale was closed and the interventricular septum showed no defect. The pulmonary artery was extremely dilated but in spite of the dilatation its wall was thicker than the aortic. Yellow plaques marred the intimal surface of the larger pulmonary arteries. On cross section, the lungs showed dilated vessels. No other gross lesion was noted.

Microscopic study showed significant lesions only in the lungs. The elastic pulmonary arteries were very large with intimal fibrous plaques occasionally containing foam cells. Small accumulations of faintly basophilic material lay between the elastic fibers, sometimes forming tiny cystic spaces. The muscular pulmonary arteries adjacent to bronchioles of all sizes were large but otherwise were normal. Arterioles in the walls of the atria and alveoli showed very prominent thickening of the vessel walls and narrowing of the lumina by medial muscular hyperplasia. In some of such arterioles, the endothelium was normal. In many others, however, cellular intimal proliferation greatly compressed or occluded the vessel lumina (Figs. 9–12). Van Gieson and trichromatic stains did not show collagen in the walls or in the endothelial plaques of these arterioles. Some of the most severely altered vessels may have been venules but the veins of the interlobular septa were normal. Recognizable organizing or organized thrombi were not found. Most bronchial arteries were normal but several of the larger ones had prominent intimal plaques significantly narrowing their lumina. Pulmonary edema was present as well as trivial lipoid pneumonia and patchy atelectasis. Muscle fibers of the right myocardium were hypertrophied.

This was the first case in which the thickening of the terminal pulmonary arterioles was recognized and led to the discovery of Case #1, as well as to interest in this rare condition.

Case 3. E. F. (J.H.H. #554109) was a two and one half year old, white boy admitted because of cyanosis. He was born after a seven months' gestation and weighed three and one half pounds at birth. Bilateral inguinal herniae were present. He was cyanotic at birth and had remained so. After the first few neonatal weeks in an oxygen tent, he improved until six months of age, since which time there had been increasing dyspnea, cyanosis and edema. On several occasions, he was treated with digitalis and mercurial diuretics. On examination, cyanosis was marked and clubbed fingers were present. The blood pressure was 120/80 in both arms. Rales were heard at the lung bases. The heart was enlarged, with a diastolic murmur heard best in the left third interspace. The pulmonary second sound was loud and split. A pulsating liver was felt four fingerbreadths below the costal margin. Anasarca was evident. A left indirect inguinal hernia was noted, and the left testicle was undescended. The red blood cell count was 8.0 million per cmm.; the hematocrit reading was 60 per cent. Before further studies could be made, the child died.

At *autopsy*, (#22727—Dr. Chamberlain), the body was well developed and well nourished with pitting edema of the lower extremities. The heart was tremendously enlarged and weighed 210 grams (normal, 60 grams), clearly the result of hypertrophy of the right atrium and ventricle. The tricuspid ring measured 7.5 cm.; the pulmonary 4.5 cm.; the mitral 5.0 cm.; and the aortic 3.5 cm. in circumference. Four normal-appearing cusps formed the pulmonary valve. The ductus arteriosus was obliterated. The foramen ovale was thought closed but a probe-patency was found which would have permitted a flow of blood from right to left. The interventricular septum was intact. The intima of the pulmonary artery was smooth but thickened. On cross-sectioning, the lungs showed dilated vessels. The liver was nodular and scarred.

Microscopic examination of the lungs showed an occasional intimal fibrous plaque in the elastic pulmonary arteries. The muscular arteries adjacent to bronchioles sometimes contained organized recanalized thrombi. One large organized thrombus was seen completely occluding the lumen of the vessel (Fig. 15). Others showed hypertrophy of the muscular walls with slight and sometimes extreme narrowing of the lumina largely the result of concentric layers of intimal proliferation (Fig. 16). These lesions were compatible with organized centrally recanalized thrombi. Tiny vessels in the atrial and alveolar walls often showed hypertrophied media and occasionally the lumina appeared narrow (Figs. 13–14). Small intimal plaques sometimes further narrowed the lumina of such arterioles. Bronchial arteries were normal as were the large pulmonary veins. Many recent hemorrhages into the air spaces were seen as well as accumulations of hemosiderin-laden macrophages. The liver showed a typical central or "cardiac" type of cirrhosis. Calcified particles in renal tubules were also seen.

Case 4. M. R. (J.H.H. A-81975) was a three year old girl who had "swelling" of the body, malaise, and anorexia of six months' duration. She had been born by caesarean section, weighing almost six pounds. Growth and development had been good. Six months previously, she had begun to vomit and lost both appetite and weight. Puffiness of the face was noted and her body became swollen. Studies for "kidney trouble" were negative. She remained listless and irritable with repeated episodes of swelling of the face and body. Exertional dyspnea and fatigability ensued and she fainted twice. No cyanosis was observed although the color of her legs was occasionally a mottled blue. On examination the blood pressure in the right arm was 128/114; the left arm 126/115; and the left leg 135/105. The recording of systemic hypertension on this occasion was possibly erroneous. On other occasions arm pressures were recorded as 90/60, 110/80, 125/100 and 100/85. She was a poorly nourished, small child with a precordial bulge. The heart was enlarged with a loud pulmonary second sound. A blowing diastolic murmur was heard along the left sternal border, maximal in the second left interspace. The lungs were clear. Minimal edema was seen but no cyanosis or clubbing. On fluoroscopy, a large right atrium and right ventricle were seen with a full pulsating pulmonary conus and pulsating hilar shadows. The lungs were clear. The red blood cell count was 6.6 million per cmm.; the hematocrit reading was 58 per cent. An electrocardiogram showed right axis deviation, high P waves, and diphasic T waves in lead II. The NPN was 44 mgm. per cent. Serological test for syphilis was positive with a titer of 1 unit. Cardiac catheterization studies did not suggest a shunt of blood and no elevation of pressure was noted. Three weeks later, however, catheter studies showed marked increases of right ventricular and pulmonary arterial pressures to 82/0 and 92/49 respectively. At the time of the second catheterization the hemoglobin was 9 grams per 100 cc. and the red blood cell count 3.6 million per c.mm. The discrepancy in red blood cell values and cardiac catheterization findings over the three-week interval was not explained and is not understood. The latter pressure readings were assumed the true values. She was transfused and discharged on digitalis. Six weeks later she was readmitted for Cortisone treatment and received 1.04 grams over a 12-day period. She died rather suddenly after complaining of vague abdominal pains and after becoming, for the first time, somewhat cyanotic.

At *autopsy* (#22941—Dr. Cochran) this well developed and well nourished child had 100 cc. of clear yellow ascitic fluid and 100 cc. of similar fluid in each pleural cavity. The heart was enlarged and weighed 120 grams (normal, 60 grams). The enlargement was the result of tremendous right ventricular dilatation and hypertrophy. The right myocardium was 0.5 cm. in thickness and the small left ventricle had a wall 0.7 cm. in thickness. The tricuspid ring measured 9.5 cm.; the pulmonary 5.3 cm.; the mitral 6.0 cm.; and the aortic 3.8 cm. in circumference. The pulmonary artery was dilated and its wall was thickened. The intimal

surface was smooth but was streaked with yellow. The aortic orifices of the bronchial arteries were not enlarged. Both the foramen ovale and the ductus arteriosus were sealed.

Microscopic abnormalities were limited to the lungs where the most striking alterations of the tiniest pulmonary vessels were noted. These vessels lay in the walls of the air spaces and were not in the immediate proximity of the terminal bronchioles. These usually thin walled capillary-like vessels here resembled systemic arterioles. The walls showed several layers of muscle cells and the ratio of total diameter to luminal diameter was markedly increased (Fig. 17). Often, intimal proliferation formed small plaques which further reduced the size of the lumina (Figs. 18–19). Elastic stains showed the internal and external elastic membranes usually to be intact but sometimes the internal elastica was frayed and lost in the plaques of intimal proliferation. The alveolar capillaries were normal. Small muscular arteries lying adjacent to the bronchioles were enlarged and showed medial hypertrophy but their lumina were not narrowed. A rare organized thrombus was seen in these arteries (Fig. 20). One artery, lying adjacent to a solitary abscess-like area in the lung, revealed an acute arteritis. This was considered as terminal aspiration pneumonia involving the artery wall rather than a primary arteritis. The elastic pulmonary arteries had flat intimal plaques of fibrous tissue with lipoid laden cells. Small accumulations of basophilic metachromic material separated the elastic fibers of the media. Areas of atelectasis were seen. Chronic passive congestion of the pancreas was present even though sections of the liver were normal.

Case 5. J. D. (J.H.H. A-70239) was a nine year old white boy who was admitted for the study of his dyspnea and cyanosis. The patient's prenatal and neonatal history was normal, and he was well until four years of age when he suffered a febrile illness diagnosed as rheumatic fever. After 15 months, by which time exertional dyspnea was extreme, the diagnosis was changed to that of congenital heart disease. At the age of six and one half years, slight cyanosis, a greatly enlarged heart with an apical thrill, pulsating hilar shadows, and pulmonary hypertension by the cardiac catheterization technique were all observed. Right ventricular pressures equalled arm pressures. Repeated episodes of cardiac failure ensued, cyanosis persisted, and he was admitted for study. The blood pressure was 85/60 in the arms and 110/70 in the legs. There was slight cyanosis and orthopnea, with dyspnea on exertion. The neck veins pulsated. The point of maximal impulse was at the anterior axillary line with an apical blowing murmur. An early diastolic murmur or a third heart sound was also heard at the apex. The lungs were clear. A pulsating liver was felt three fingerbreadths below the costal margin. No edema was noted. Fluoroscopy revealed a prominent pulmonary artery and a large right heart with pulsating hilar shadows. The EKG showed right axis deviation. The red blood cell count was 6.5 million per c.mm. and the hematocrit was 54 per cent. Arterial oxygen saturation at rest was 70 per cent; after breathing oxygen it was 85 per cent. Cardiac catheterization studies indicated a low systemic blood flow, a low pulmonary blood flow, and a right ventricular pressure of 110/20. A large right-to-left shunt was also obvious. The child died suddenly during injection of diodrast for angiocardiography.

The *autopsy*, (#21820—Dr. Eversole), revealed a well developed and well nourished, white male without peripheral edema but having clubbed fingers. The significant findings included an enormously enlarged heart which was the result of right atrial and ventricular hypertrophy and dilatation. It weighed 450 grams (normal, 120 grams). The foramen ovale was anatomically patent and, although covered by a valve, would have been functionally patent with the dilatation of the heart and the high right atrial pressure. The right ventricle wall measured 1.5 cm. in thickness; the left ventricle 1.0 cm. The circumference of the tricuspid valve ring was 10 cm.; the pulmonic valve 6.8 cm.; the mitral 6.5 cm.; and the aortic, not measured, was thought normal. The main pulmonary artery and branches were en-

larged and the walls were thicker than normal. Yellow intimal plaques were present. The ductus arteriosus was closed. No other malformation of the heart was noted. A prominent muscular "moderator" band crossed the right ventricular chamber. Sections of the lungs revealed excessively prominent pulmonary vessels. The aortic orifices of the upper intercostal and bronchial arteries were enlarged.

Microscopic abnormalities were limited to the lungs. The tiniest of pulmonary vessels, those lying in the walls of the air spaces, occasionally showed thickened and hyaline walls with narrowed lumina but these vessels were usually normal. The small and medium sized arteries lying adjacent to terminal bronchioles revealed extraordinary changes consisting of intimal proliferation which often narrowed the vessel lumina to pinpoint size, even to occlusion (Figs. 22–23). Some of the lesions were old and hyaline, others suggested organized thromboses and definite organized and recanalized thrombi were seen in other vessels. One artery with a more recent recanalized thrombus was found to be involved by a mild inflammation of the vessel media and adventitia (Fig. 21). Elastic tissue stains showed that several vessels exhibited a focal replacement of the arterial wall by fibrous tissue. These lesions seemed characteristic of healed arteritis (Figs. 22 & 24). Medial muscular hypertrophy, occasional adventitial thickening, and frequent splitting of the internal elastica of the small muscular arteries were also seen. The larger elastic pulmonary arteries showed flat lipoid laden intimal plaques. In the media of such vessels, basophilic metachromatic material separated the elastic fibers. No emphysema or other parenchymatous disease was seen in the lungs. No lesion suggesting rheumatic fever was seen in the myocardium or cardiac valves.

Case 6. L. B. (J.H.H. A-71540) was a three year old, white female admitted for cyanosis and dyspnea since birth. There had been no maternal illness during pregnancy. The cyanosis increased during exercise. She had been studied previously and a diagnosis of pulmonary stensosis had been made. She was seen as a thin, undernourished girl, cyanotic at rest, with clubbed fingers and toes. The point of maximal impulse was in the anterior axillary line with a systolic thrill over the precordium and a harsh systolic murmur over the chest and back. There was a loud, clear pulmonary second sound. The lungs were clear. A non-pulsating liver was felt three fingerbreadths below the ribs. On fluoroscopy, the heart was large with a full pulmonary conus. The lungs were clear. The hilar vessels appeared to pulsate. The red blood cell count was 6.8 million per c.mm.; the hematocrit was 57 per cent. With a diagnosis of pure pulmonic stenosis but with a suspicion of primary pulmonary hypertension, thorocotomy was performed. Heart action became poor and the child died.

Autopsy, (#22338—Dr. Eversole), disclosed a well developed and well nourished child without edema, ascites, or clubbed fingers. The heart was greatly enlarged and the right ventricle was estimated to be two or three times the size of the left ventricle. The foramen ovale was patent and its orifice measured 0.6 cm. in its greatest diameter. The ductus arteriosus was closed. Cardiac measurements showed a 0.9 cm. right ventricular wall and a 0.5 cm. left ventricular wall. The circumference of the tricuspid valve was 8.5 cm.; the pulmonary 4.5 cm.; the mitral 6.3 cm.; and the aortic 3.4 cm. A muscular "moderator" band extended across the right ventricular chamber. Enlarged orifices of the bronchial and upper intercostal arteries were encountered in the thoracic aorta and the greatly enlarged bronchial arteries were traced into the lungs.

Microscopically, many small pulmonary arteries, lying adjacent to small or terminal bronchioles, were severely altered by intimal proliferation which led to virtual occlusion of many vessels (Figs. 25–27). These lesions were characteristic of completely organized recanalized thrombi. Medial or elastica changes were usually trivial but occasionally medial scarring was present. Adventitial scarring was often prominent. In the lumina of the slightly larger arteries, organizing or completely organized and recanalized thrombi were also numer-

ous (Fig. 28). Most of the muscular arteries showed medial hypertrophy but this change did not perceptibly affect the lumina of such vessels in the absence of other changes. The vessels lying in the walls of the atria and alveoli were normal. The largest of elastic pulmonary arteries showed intimal fatty plaques. Very slight emphysema seemed apparent in the lungs. Recent hemorrhages were noted in the pulmonary alveoli.

Case 7. W. W. (J.H.H. A-87550) was a five and one half year old, white girl who was admitted because of vomiting, dyspnea, and epigastric pain. She was always a feeding problem, occasionally vomited, and had failed to gain weight properly. For six months anorexia had increased and she had lost weight. For three months dyspnea on exertion had been observed. Two weeks before admission a "cold" was accompanied by fever, cough, nausea, and vomiting. This improved but severe epigastric pain with nausea, vomiting and extreme dyspnea developed. No cyanosis had ever been noted.

She was a poorly nourished, pale child without cyanosis. The heart was enlarged. The cardiac sounds were of good quality with a loud, banging pulmonic sound, a long, loud, harsh diastolic murmur along the left sternal border and an apical gallop rhythm. By fluoroscopy, the heart was enlarged to the right and left with pulsating pulmonary conus and hilar shadows. The EKG showed right axis deviation. The red blood cell count was 4.0 million per c.mm. with a hematocrit of 41 per cent. The venous pressure was 100 mm. of water and the arm-to-tongue circulation time was 15 seconds. Cardiac catheterization showed a pressure of 131/11 in the right ventricle and 105/42 in the pulmonary artery. No evidence of a right-to-left shunt was obtained. In spite of oxygen, digitalis, and antibiotics, she failed to improve and anorexia, precordial pain, and dyspnea continued. She died following a convulsion.

Autopsy, (#23243—Dr. Andrews), showed a thin, poorly developed child without peripheral edema or ascites. The heart was enlarged due to right ventricular hypertrophy and dilatation and weighed 180 grams (normal, 95 grams). The foramen ovale was sealed shut as was the ductus arteriosus. The pulmonary arteries were thick-walled and dilated with an occasional yellow intimal plaque. No abnormality was noted on cross sections of the lungs. The orifices of the bronchial arteries were normal in size. Cardiac measurements included a right ventricular myocardium of 0.8 cm. with the left of 0.7 cm. The tricuspid valve circumference was 9.5 cm.; the pulmonary 4.5 cm.; the mitral 6.0 cm.; and the aortic 4.0 cm. Just above the pulmonary valve the artery measured 6.0 cm. in circumference while just above the aortic valves the aorta measured 4.0 cm.

Microscopic sections of the lungs showed numerous thrombi in the small pulmonary arteries (Figs. 29–30). These were usually in the muscular arteries lying adjacent to bronchioles. Many of the thrombi were in various stages of organization from completely recanalized fibrotic lesions (Fig. 34) to those showing only beginning invasion by endothelial cells (Fig. 29). Some very small arteries showed concentric rings of intimal fibrosis which probably represented old organized thrombi resembling arteriosclerosis (Fig. 35). An occasional artery had leucocytic infiltrations of the media and adventitia (Figs. 31–32). These were largely mononuclear but a rare polymorphonuclear was present and several eosinophiles were seen. Definite necrosis with nuclear fragmentation of the muscular wall was seen in one artery (Fig. 33). Elastic stains of this vessel, as well as of several of the old organized thrombosed vessels, showed destruction of the intimal elastic lamellae. The tiny vessels lying in the walls of the air spaces were for the most part normal although an occasional vessel in this location showed intimal proliferation leading to narrowing of the lumen. The largest or elastic pulmonary arteries had lipoid intimal plaques, and faintly basophilic metachromatic material separated the muscle and elastic fibers of the media. No inflammatory disease of the lungs, no scarring and no emphysema were encountered. Chronic passive congestion of the pancreas was seen.

Case 8. S. S. (J.H.H. A-82708) was a fifteen months old, white girl admitted for increasing dyspnea and cyanosis. There were no neonatal difficulties until three months of age when she failed to gain weight. At five months of age a heart murmur was heard and three x-ray treatments were given for an "enlarged thymus." At seven months of age the patient was studied here for failure to gain weight. A dusky hue had been noted as well as a systolic thrill at the apex. The heart was large. A loud, harsh systolic murmur was heard over the precordium, maximal along the left sternal border. Fluoroscopy revealed a convexity in the region of the pulmonary conus. The EKG showed a right axis deviation. The red blood cell count was 5.7 million per c.mm. and the hematocrit was 43 per cent. No cardiac failure was noted. On examination, during the final admission at the age of 15 months, a dyspneic, slightly cyanotic infant was seen. The heart was large, a systolic thrill was felt along the left sternal border, and a harsh systolic murmur was heard in the same area. There was clubbing of the fingers and toes. A pulsating right atrium and pulmonary conus was noted on fluoroscopy. The red blood cell count was 7.5 million per c.mm.; the hematocrit was 55 per cent. Angiocardiography demonstrated an interatrial communication with a dilated pulmonary artery and a delay of emptying of the pulmonary artery. The child was explored for a pulmonic stenosis and a high pulmonary artery pressure was obvious. She died shortly after operation.

At *autopsy*, (#23268—Dr. Cochran), a well developed and well nourished child was without edema or ascites. The heart was enlarged, weighing 70 grams (normal, 46 grams). Right ventricular hypertrophy was prominent; the left ventricle appeared small in comparison. The foramen ovale was patent, measuring 1 cm. in diameter, but was partially covered by a valve flap. The pulmonary arterial wall equalled the aorta in thickness but no yellow intimal plaques were seen. The ductus arteriosus was closed. The right ventricular wall measured 0.5 to 0.8 cm. in thickness while the left varied from 0.2 to 0.5 cm. The circumference of the tricuspid valve measured 6.5 cm.; the pulmonary 3.2 cm.; the mitral 5.0 cm.; and the aortic 3.0 cm. Just above its valve the pulmonary artery measured 4.2 cm. in circumference while the aorta measured 3.1 cm. The orifices of the bronchial arteries in the aorta were not enlarged. A Meckel's diverticulum of the terminal ileum was found.

Microscopically, the only changes were found in the lungs where lesions were confined to the pulmonary vessels. The tiniest pulmonary vessels which lay in the walls of the air spaces were dilated but otherwise normal. Small muscular arteries, adjacent to terminal bronchioles, contained prominent thrombi of varying ages and extent of organization and recanalization (Figs. 37–38). In many the lumina were greatly narrowed by the process. Other vessels in the same location showed intimal proliferation and splitting of the elastica and presented an appearance indistinguishable from primary arteriosclerosis (Figs. 39–40). The largest or elastic pulmonary arteries disclosed prominent lipoid deposits in the intima. Slightly basophilic metachromatic material was seen between the medial elastic fibers in these vessels. No active arteritis was seen but some of the recanalized thrombosed arteries showed loss of the medial structure with adventitial scarring compatible with a healed arteritis. No pulmonary parenchymal disease was seen other than small foci of lipoid pneumonia.

Case 9. J. M. (J.H.H. A-99364) was a one year old, white male infant admitted for generalized edema. The patient was born of an eight months' pregnancy, weighing 3 pounds and 6 ounces. He was kept in an incubator for the first month of life and never appeared well. He showed a poor weight gain, persistent rapid respirations, and anorexia. He vomited frequently. Three weeks before admission edema of the ankles and face developed and he was treated successfully with digitalis. The edema recurred. After an upper respiratory tract infection, a severe cough appeared and he was admitted to the hospital.

On admission, he weighed 11.5 pounds, had a temperature of 98.6°F., a pulse rate of 140

per minute, and a respiratory rate of 32 per minute. The systolic blood pressure was 105 in the right arm and 100 in the right leg. There was no cyanosis. Edema of the face and ankles was seen and rales in the lungs were heard. The heart sounds were of poor quality, a gallop rhythm was present, and a soft systolic murmur was heard over the precordium. The pulmonary second sound was not loud. The liver was two fingerbreadths below the costal margin. By fluoroscopy, the heart was large with an active pulmonary conus but without prominence of the pulmonary arteries. No hilar pulsations were noted. The vascularity of the lung fields was diminished. In the oblique views, the right ventricle appeared enlarged. The hemoglobin was 12 grams per 100 cc., the red blood cell count was 5.47 million c.mm., and the hematocrit was 40 per cent. The EKG showed a right axis deviation. A probable diagnosis of Ebstein's anomaly was made but to exclude the possibility of pulmonary stenosis, cardiac catheterization was done. The right ventricular pressure was found to be 95/12 and the right atrial pressure 8/2. The catheter could not be passed into the pulmonary artery. There was no evidence of a shunt but indications of an extremely low cardiac output was noted. The child suffered sudden cardiac arrest shortly after the catheterization and died despite cardiac massage.

At *autopsy*, (#24126—Dr. Mark), the body was well developed and well nourished. Cyanosis of the limbs was seen but no clubbing was noted. No edema or fluid in the body cavities were seen. The heart weighed 180 grams (normal, 44 grams). The foramen ovale was sealed and the ductus arteriosus was closed. No valvular or endocardial lesion was noted. The huge right ventricle had a myocardial wall of 1.0 cm. thickness while the relatively tiny but probably normal left ventricle had a wall 0.8 cm. in thickness. The pulmonary artery was as wide and as thick-walled as the aorta. The lungs were normal save for dilatation of the hilar arteries. No other gross lesion was seen.

Microscopic abnormalities were confined to the lungs. The small pulmonary arteries lying adjacent to the terminal bronchioles and alveolar ducts often showed very severe narrowing of the lumina by hyaline intimal deposits or cellular intimal proliferation (Figs. 41–44). Some were clearly organized thrombi; most were not so identifiable. The arterioles lying in the walls of the air spaces occasionally showed prominent medial hypertrophy which narrowed the lumina. Intimal poliferations were also found in these tiny vessels. (Figs. 45–47). Acute changes with nuclear fragmentation in the media of one small arteriole was altogether similar to that seen in systemic malignant hypertension (Fig. 48). The large muscular and elastic pulmonary arteries were normal save for dilatation and hypertrophy. No pulmonary parenchymal disease was seen.

DISCUSSION

In all nine cases, stenosing pulmonary vascular lesions have been found in the absence of other known causes for pulmonary hypertension and right ventricular hypertrophy. While severely narrowed arteries such as these must impede blood flow, there is no way of determining by histological methods how many vessels must be so narrowed to lower the capacity of the pulmonary vascular bed to that level at which persistent hypertension will occur. When vascular lesions are severe and widespread in histological sections which are taken from each lobe of the lungs, it seems reasonable to suspect that the same lesions are distributed in a similar concentration throughout the lungs. Vascular changes are often focal in character, and a stenosing lesion capable of causing a significant obstruction to blood flow may involve only a short segment

of the artery. Sections proximal or distal to the lesion might have shown a normal vessel. This further increases the significance of finding obstructing lesions in many vessels in the routine sections. It seems therefore clear that the stenotic vascular changes which have been found frequently in sections of the lungs of these patients were of significance in the origin or at least in the persistence of the pulmonary hypertension, for we do not know that such lesions antedated the hypertension.

Certain of the pulmonary vascular lesions were common to all cases and differed only in degree. These are lesions usually considered to be a result of hypertension. Arteriosclerosis of the elastic arteries, which is characterized by intimal foam cell accumulation and intimal fibrosis, was seen in all. This may be found in all varieties of pulmonary hypertension. In addition, there was an enlargement of pulmonary arteries of all sizes. These vessels, which lie adjacent to the bronchial tree, were often seen to be as large, or even larger, than the associated bronchus or bronchiole. In the normal lung (Figs. 1, 2), the diameter of the arteries is nearly always considerably smaller than that of the adjacent bronchiole (7). The walls of these arteries were also often hypertrophied, but this did not result in appreciable narrowing of the vessel lumen.

The lesions which unequivocally narrowed the arterial or arteriolar lumen seem broadly divisible into two basic groups. This histologic separation is apparent in spite of the fact that no essential differences were noted in the clinical progress of the disease. Such a separation may be of importance in arriving at the pathogenesis of a single clinico-pathological entity or, more likely, may only emphasize the obvious fact that different pathological processes may lead to similar functional changes.

In five cases (1, 2, 3, 4, and 9) prominent vascular alterations were found in the pulmonary arterioles. These precapillary vessels are those which lie in the walls of the atria and alveoli. In the normal lung, arterioles are extremely thin-walled structures and are distinguished from venules or even capillaries with great difficulty (Figs. 3 and 4). Miller (7) prefers not to employ the term "arterioles" for the arterial branches which lie in the walls of the atria and alveoli and which divide into the pulmonary capillaries. It is convenient, however, to separate by name these normally very thin-walled vessels from the muscular arteries which traverse the lung immediately adjacent to normal respiratory bronchioles and alveolar ducts. The sudden origin of very thin-walled arterial branches from relatively thick muscular arteries is unique to the normal lung in contrast to the gradual reduction in thickness of the walls of successive branches of systemic arteries. The precapillary arterioles of the lungs of these five patients with pulmonary hypertension often resembled arterioles of the systemic circulation where the pressures are normally at the level which existed abnormally in the lungs of these patients (Figs. 5–8). The external diameter of many arterioles was comparable to that of normal vessels

in the same location so that the reduction in luminal diameter could not have been the sole consequence of contraction. In others, contraction was also evident from the wrinkled appearance of the endothelium and internal elastica. Whether solely the result of medial hypertrophy and hyperplasia or the combined result of these and contraction of the vessel walls, such vessels were not seen in sections of lungs prepared by identical techniques from children of the same ages who had died without cardiovascular or pulmonary diseases.

In these same five cases, endothelial proliferation, which often suggested organized thrombi, was also found to contribute to the *arteriolar* stenosis (Figs. 9–12). These lesions were seen rarely in three cases and frequently in two cases; they seemed to be acquired lesions although their pathogenesis is unknown. Finally, in Case #9 an occasional arteriole resembled the hyaline or even the necrotic arteriole of systemic hypertension (Figs. 47 and 48).

The origin of the arteriolar lesions unfortunately has remained obscure. Kamp and Dry (8) have mentioned and Civin and Edwards (9) have emphasized that the small arteries of newborn infants show an increased ratio of thickness of wall to luminal diameter as compared to older children or adults. After birth this is rapidly lost so that in normal infants of three or four months of age the vessels are very thin-walled structures resembling venules or even capillaries (Figs. 3 and 4). The muscular neonatal vessels have been thought to be responsible for shunting of blood away from the lungs during fetal life. Changes in blood oxygen saturation may also influence the pulmonary vascular resistance in the fetus and newborn infant. (10, 11).

Arteriolar lesions similar to those we are reporting have also been described, with or without thrombi, in association with certain congenital malformations of the heart such as Eisenmenger complex (12), coarctation of the aorta associated with a patent ductus arteriosus (13), and cor triloculare biatrium with wide pulmonary and narrow aortic outlets (14). We have also found similar changes in such cases as well as in some patients who died with transposition of the great vessels, anomalous return of pulmonary venous blood to the right heart, and rarely in cases of very large interatrial or interventricular septal defects. In all of these anomalies, a very large flow of blood is directed through the lungs. In all, a diversion of blood from the lungs to the systemic circulation might be physiologically beneficial. It has, therefore, been suggested by Edwards (15) that in these cases of cardiac malformation, the arteriolar hypertrophy might represent a preservation of the prenatal and early neonatal vascular structure. The experimental work of Muller and Dammann (16) suggests also that arteriolar hypertrophy may be an *acquired* result of an increase of pulmonary blood flow. These authors showed that after one year a large shunt of arterial blood at aortic pressures through one lung of a dog resulted in slight but definite medial hypertrophy of pulonary arterioles. One of their illustrations (Fig. 5-c) showed arteriolar contraction and medial hypertrophy

entirely similar to changes which we have described in the above five cases. Valenzuela et al. (17) have recently described and beautifully illustrated thick-walled muscular arterioles in the lungs of a patient with tetralogy of Fallot and a large shunt of blood from the aorta into the lungs.

No cardiac malformation or cause for initially increased pulmonary blood flow could be found in our cases. Anatomical patency of the foramen ovale was found in two of these five cases but the opening was quite small and even though accentuated by the right atrial dilatation which was present, was anatomically not of a size greater than that seen in perhaps 30 per cent of all autopsies on patients in this age group. The size of the foramina and the overlapping septa indicated clearly that the opening had assumed physiological significance only *after* right atrial pressures had become elevated and *after* right atrial dilatation had developed.

While it thus appears that there was no obvious cause for an increase of pulmonary blood flow in these cases, functional arteriolar contraction of obscure etiology which led to pulmonary hypertension and thence to hypertrophy of the arteriolar walls remains a possible cause for the vascular changes. Some of the vascular lesions, especially those in Case 9, are suggestive of those which result from hypertension. It would be quite reasonable to find hypertrophy of thin-walled vessels after prolonged contraction of the muscular wall. Schmidt (18) believes that increased vasomotor tone in the pulmonary vessels including the veins led to the pulmonary hypertension and thence to the vascular lesions seen in the large series studied by him, although the etiology of the increased tone was not elucidated. That the pulmonary vascular bed is a dynamic system is now well recognized. Many workers have shown in animals (19) and in humans (10, 11) that anoxia results in an increase in pulmonary arteriolar resistance. Others have demonstrated many pharmacological agents which alter the resistance in the pulmonary vascular bed in normal or diseased patients (20). No primary cause for anoxia was found in our patients and a functional increase of vasomotor tone antedating the morphological lesions remains unproven. It is somewhat substantiated, however, by the relatively infrequent vascular lesions in Case 3 in spite of the severe clinical symptoms which began at birth. Two adults with pure pulmonary hypertension who had rather insignificant pulmonary vascular lesions have been described by de Navasquay et al. (21).

While hypertrophy of the media of pulmonary arterioles might be secondary to hypertension, the cellular intimal plaques seen in the same five patients of our series are more likely primary lesions. These lesions often were suggestive of organized thrombi but the origin of such thrombi was not determined.

Schmidt (18) considered that an increased vasomotor tone in the veins led to the pulmonary hemorrhages and signs of chronic passive congestion seen in

some of his cases. The hemorrhages and hemosiderin-laden macrophages found in three of our cases are perplexing in patients with otherwise pure rightsided heart disease. While the muscular peribronchial vessels are clearly arterial, it is possible that some of the lesions in the tiny vessels in the air space walls were venous. Certainly larger veins in the lobular septa were normal and reexamination of several hearts showed no changes of the large pulmonary veins in the hila of the lungs or at the left atrium.

Finally, that some unknown congenital defect in the structure of the pulmonary vessels led to the vascular changes finally seen in these children remains a remote possibility. Two of the five cases had other vascular malformations; a bicuspid aortic valve and slight coarctation of the aorta in Case 2 and four cusps in the pulmonary valve of Case 3.

Pulmonary arteriolar changes similar to these have been described by Wolman (22) in two infants who were cyanotic at birth. These patients only survived six weeks and one day respectively but Wolman showed that the changes were greater than could be found in the normal lungs of infants of similar ages. Recently Parmley and Jones (23) have reported three adults with cor pulmonale and pulmonary vascular lesions. While their second case was more likely the result of emphysema, the arteriolar lesions found in their first case, a 26-year-old woman, closely resembled those seen in the five cases described above. Photomicrographs of the vascular lesions seen in that patient also include obvious organizing arterial and arteriolar thrombi.

In our first four cases, the small muscular arteries which lay adjacent to bronchioles showed some medial muscular hypertrophy without reduction of lumina. Arterial intimal changes were seen occasionally in Cases 3 (Fig. 16) and 4, but were frequent and severe in Case 9 (Fig. 41). In the latter, the intimal arteriosclerosis was surely severe enough to contribute significantly to the increase in resistance to blood flow. The three cases with arteriosclerotic lesions were those in which occasional thrombi were present in arteries of a similar size. It is our belief that these arteriosclerotic-like lesions were actually a result of organized thrombi or of intimal proliferation adjacent to such thrombi.

Arteriolar lesions were insignificant or absent in Cases 5, 6, 7, and 8. These cases showed, as did Case 9 and to a much less extent, Case 3, severe lesions of the small muscular arteries which lie adjacent to terminal bronchioles or respiratory ducts (Plates VI–XI). Thromboses in all stages of repair or severe intimal arteriosclerosis were present in these vessels. It was often extremely difficult, if not impossible, to separate these two processes. It is well recognized from human autopsy study and it has been demonstrated experimentally (24, 25) that pulmonary thrombi may organize in such a way as to mimic exactly primary arteriosclerosis. While it cannot be denied that thrombi may form upon altered endothelium which results from a primary arteriosclerosis,

it is thought that the pulmonary vascular thrombi in these cases probably constituted a primary lesion, and either occurred together with arteriosclerosis, or, much more likely, led to the arterisclerotic-like lesions.

The origin of the thrombi unfortunately also remains obscure. An arteritis may have been occasionally responsible. In Case 7, an acute arteritis, apparently more severe than would be instituted by a bland thrombosis alone, was present (Fig. 33). While only four or five such lesions were seen, it remains a remote possibility that a sporadic focal arteritis of unknown etiology could have resulted in the thromboses in this case. In Case 5 the thrombi were quite old and often completely organized, but several of these were associated with completely healed destruction of the arterial walls which were quite compatible with a healed necrotizing arteritis (Fig. 24). While such lesions are rare in the pulmonary vascular bed, definite instances are known to occur. A postmortem examination in this laboratory on a 45-year-old woman dying with cor pulmonale disclosed a unique widespread acute necrotizing pulmonary arteritis in association with thrombus formation and prominent intimal changes which, although clearly the result of the arteritis and organizing thrombi, mimicked primary arteriosclerosis. Similar cases have been described (4). Bland pulmonary emboli, however, may result in the development of a mild local arteritis in the absence of any primary pulmonary vascular disease. Muirhead (26) has described such lesions in autopsy material and in experimental embolization. Emboli containing foreign material such as cotton fibers may also cause a severe local arteritis (27). No such material was seen in the semi-serial sections made of the arteritic lesions in our cases and, in our experience, in the absence of foreign bodies, parasites, pulmonary parenchymal disease or rheumatic fever, pulmonary vascular thrombi are not associated with an arteritis as severe as that seen in Case 7 nor, when organized, with the appearance of a healed destruction of the arterial wall as was seen in Case 5. The stenosing vascular lesions in the latter case are very likely the consequence of healed pulmonary arteritis, the specific nature of which is now obscure.

A number of cases have been described in the literature in which pulmonary thrombi have led to hypertension and cor pulmonale. Most of these reports have described thrombi lodged in the major pulmonary arteries where the effect has been essentially similar to pulmonic stenosis (6). Several cases have also been reported in which thrombi in smaller muscular arteries have led to the syndrome of pulmonary hypertension (2, 3). All cases so far located in the literature have occurred in adults in whom occasionally the source of the thrombi from phlebothrombosis has been demonstrated (28). Phlebothrombosis is, of course, an exceedingly rare disease in infancy and childhood and thromboembolic phenomena in this age group are very unusual (29). No history suggesting umbilical vein thrombosis at birth was noted in our patients but this structure was never specifically studied at autopsy. Thrombosis of the vena

cava was not found. The source of the pulmonary thrombi in all of our cases thus remains obscure although the possible role of polycythemia must be discussed.

The presence of cyanosis in six of the nine cases is of particular interest. In none were changes in the alveolar walls or capillaries noted. Emphysema, found in several microscopic sections, was trivial and possibly was related to the anesthesia of operation. In order for cyanosis to occur as a result of alterations of diffusion of oxygen across the alveolar membrane, a relatively large proportion of capillary bed must be lost (30), certainly not the situation in any of the cases. It is, therefore, difficult to understand how chronic cyanosis could develop purely on a basis of increased arterial or arteriolar resistance unless such resistance led to vascular shunts. It is not possible to prove the presence or absence of *intrapulmonary* arteriovenous shunts in any of the cases. That such may exist normally in the lung has been demonstrated (31, 32) and it would be thought that in the presence of increased pulmonary arterial pressures communications from right-to-left would be more apt to function and to enlarge. Yet if such intrapulmonary shunts were responsible for the cyanosis in these cases, three of the patients did not possess them. Cases 4, 7 and 9 had no cyanosis yet demonstrated equally severe evidence of pulmonary hypertension. These three cases had pulmonary vascular lesions equal in severity to or greater than those of the cyanotic cases. One might postulate that the vascular stenosis in the three acyanotic patients had occurred proximal to the usual site of the arteriovenous shunts; in one acyanotic case, however, the vascular changes were primarily in the *terminal* arterioles.

All patients with a persisting cyanosis had, however, an anatomical patency of the foramen ovale. At least two of the six patients had relatively large patencies, although neither could be considered interatrial septal defects. Another, with cyanosis dating from birth, only had a 0.2 cm. defect. Although it is difficult to believe that this defect was large enough to allow a shunt of blood from right-to-left to cause cyanosis, the cyanosis had been mild until two years of age, by which time polycythemia had become more severe and the cyanosis only then became intense. The size of the patency in the other three cases was not clearly stated. It is noteworthy that anatomical patencies of the foramen ovale may be covered by a wide flap. The flap or valve covering the defect is usually located in such a way that a high right atrial pressure would result in a right-to-left shunt. In Case 2 there was a history of cyanosis occurring in attacks. The autopsy protocol of this cast stated that the foramen was "closed" but no mention was made of gently probing for a concealed opening.

Catheterization studies indicate that patients with "primary" pulmonary hypertension may exhibit a very low cardiac output (33). That this might result in a peripheral cyanosis is also possible and probably accounts for the transient attacks of cyanosis in Case 2. It is difficult to understand on this

basis alone, however, the absence of cyanosis in three of the cases whose cardiac status seemed entirely similar to the others.

Polycythemia was present in all cases with persistent cyanosis. The development of polycythemia would aggravate cyanosis, yet it cannot be considered a primary cause of that cyanosis. No reason for the development of polycythemia other than a right-to-left vascular shunt was recognized. Those patients without an anatomical patency of the foramen ovale failed to develop polycythemia even though the pulmonary hypertension was equally severe. The combined factors of a right-to-left shunt, polycythemia, and a reduced cardiac output all may be essential for the development of persistent cyanosis in these patients.

The observation of cyanosis from birth in two of the patients might indicate that pulmonary hypertension and hence a right-to-left shunt was already present at birth. It suggests that either the pulmonary lesions were of a congenital origin or that a functional pulmonary hypertension was already present at birth which eventually resulted in the morphological lesions later seen at autopsy. Both of these patients had a small anatomical patency of the foramen ovale. One was 0.2 cm. and the other 0.6 cm. in diameter. The first, Case 3, showed the least prominent vascular lesions of the entire series. These were in small arteries and in the terminal arterioles. The second, Case 6, had prominent arteriosclerotic lesions of the muscular arteries. These vessels also contained thrombi but there were no changes in the terminal arterioles.

As mentioned, polycythemia accompanied all cases with persistent cyanosis and was transiently present in one of the acyanotic patients. It was not noted in the child who developed cyanosis only with paroxysmal attacks of dyspnea. An invariable association between the existence of polycythemia and the pulmonary thrombi would have helped to explain the origin of the thrombosis. Rich (34) has emphasized the probable importance of polycythemia, acting in concert with the reduced pulmonary blood flow, in the pathogenesis of the thrombi which he discovered in a high percentage of children with tetralogy of Fallot. But, in our Case 7, there was no patent foramen ovale, no polycythemia and no cyanosis, yet extensive pulmonary vascular thrombi were present. Furthermore, the pulmonary vascular thrombi in four cases seemed to be the major cause of the pulmonary hypertension and thus the cause of the right-to-left shunt which led to the polycythemia itself!

Finally, hypertension may have initially been a physiological abnormality which then resulted in all of the observed morphological changes. A "functional" hypertension may also explain arterial necrosis. A rapid rise of intraluminal pressure in the systemic circulation is thought to be the cause of the arteriolar sclerosis and necrosis which are seen in both human and experimental systemic hypertension (35). It has been considered that hypertension may cause damage to the endothelium and vessel wall with an exudation of plasma or even of red blood cells and leucocytes into the walls of the arterioles. Necrosis

of arterial walls has been observed in pulmonary arteries in cases where the pulmonary hypertension seemed to be initially a result of cardiac disease. Old and Russel (36) and Kipkie and Johnson (37) have reported cases of necrotizing pulmonary arteritis in patients with Eisenmenger complex. Symmers (38) and Hicks (39) have each described such lesions in chronic mitral stenosis and we have seen similar cases in this laboratory.

It is apparent that this morphological study of nine children with pulmonary hypertension has not uncovered the basic disease process or processes which led to that hypertension or to the pulmonary vascular lesions found at autopsy examination. Whatever the pathogenesis, however, it seems clear that the vascular lesions in these cases were sufficiently frequent and severe to at least result in a persistence if not in the etiology of the eventually fatal pulmonary hypertension. That such hypertension would be irreversible is not so obvious for while most of the vascular lesions seen would hardly be expected to resolve, those dependent upon hypertrophy and hyperplasia of the arteriolar muscle might well be reversible. Information concerning the possible existence and consequences of a persistent increase of vasomotor tone of the pulmonary vascular bed is essential to the final understanding of the vascular lesions found in these cases.

SUMMARY

Nine cases of pulmonary hypertension in infants and children have been described. No cardiac malformation which might have resulted in large increases of pulmonary blood flow was present. The only apparent cause for the hypertension in all nine cases was the pulmonary vascular lesions. These consisted of arteriolar hypertrophy and intimal plaques, intravascular thrombi, and arteriosclerosis. Many of the arteriosclerotic-like lesions were thought to be the result of completely organized recanalized thrombi. The development of pulmonary vascular thrombi seemed of major importance in most cases. The origin of the thrombi was obscure although evidence of pulmonary arteritis was present in two cases. No lesion of the vessels of the systemic circulation was seen. The polycythemia present in six patients could not be convincingly proven as the primary cause of the intravascular thromboses. Cyanosis and polycythemia were thought to be the consequence of the pulmonary hypertension and a small patent foramen ovale. A better understanding of pulmonary vasomotor activity may do much to explain the extensive pulmonary vascular lesions seen in these cases.

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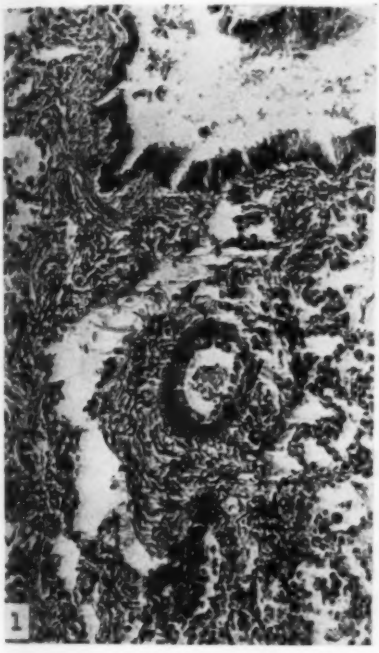
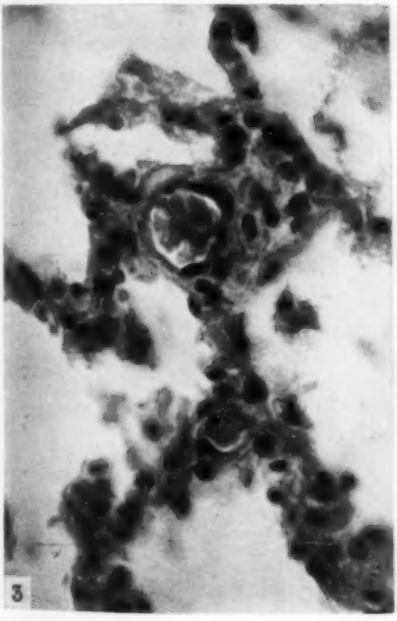
PLATE I—Normal lung vessels from infants

FIGS. 1 and 2. Small pulmonary arteries lying adjacent to bronchioles. Diameter of arteries considerably less than that of bronchioles (low power).

FIGS. 3 and 4. Arterioles (or venules) in air space walls ((high power).





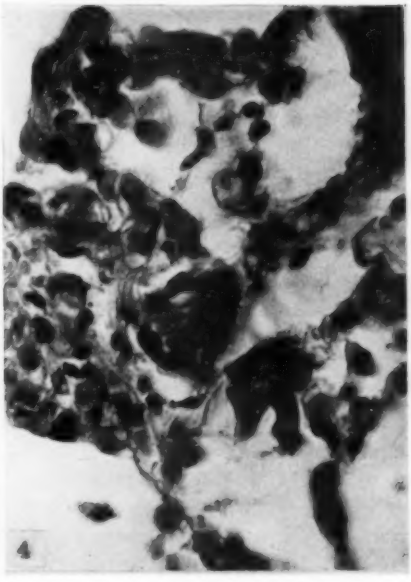
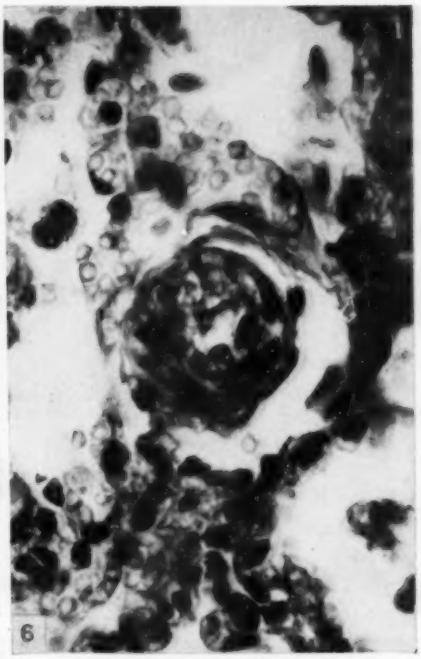
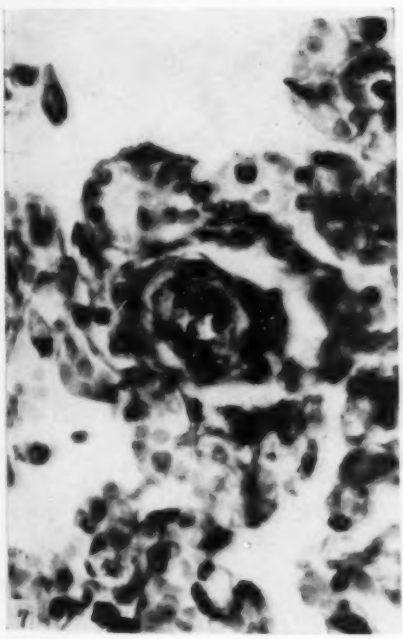


PLATE II—Case 1

FIGS. 5–7. Hypertrophy of walls of arterioles in alveoli (high power).

FIG. 8. Slight wrinkling of internal and external elastic layer suggesting contraction of arteriole in alveolar wall (elastic stain; high power).





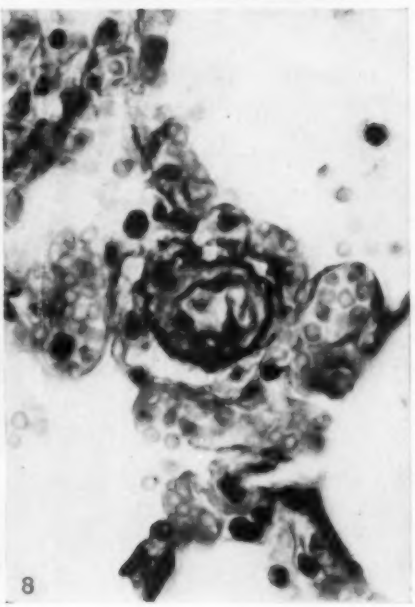


PLATE III—Case 2

FIGS. 9–11. Intimal plaques severely narrowing arteriolar lumina (high power).
FIG. 12. The same in an elastic tissue stain (high power).

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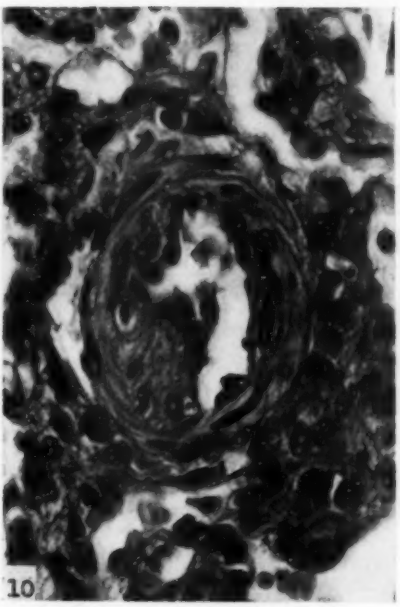

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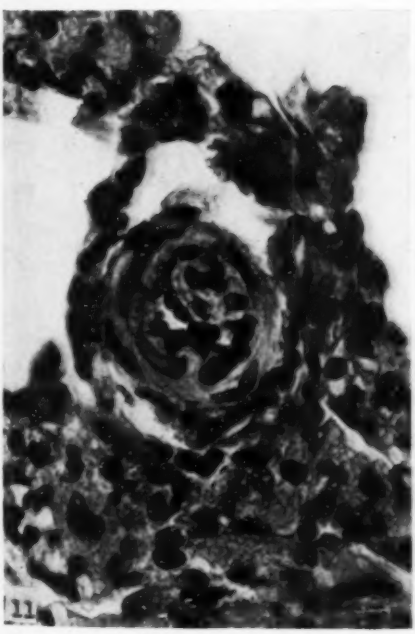

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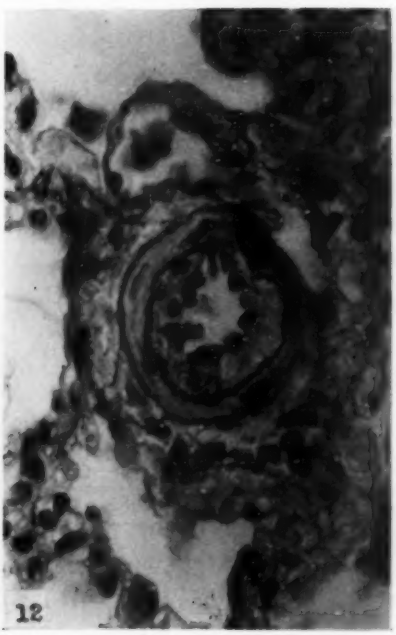

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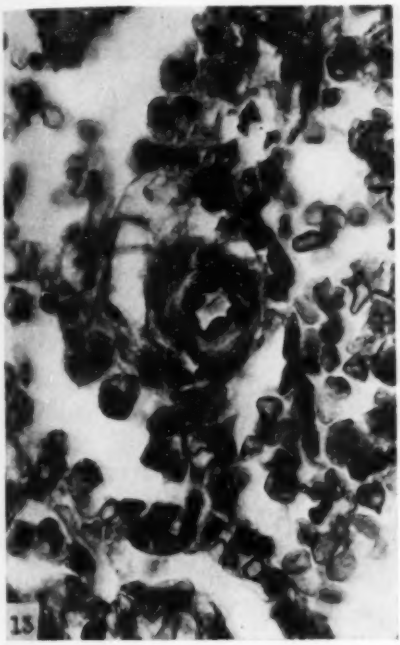
PLATE IV—Case 3

FIGS. 13 and 14. Arteriolar hypertrophy in alveoli (high power).

FIG. 15. Intimal proliferation and scarring in artery, compatible with organized thrombus. Note size of artery in comparison to bronchiole (low power).

FIG. 16. Marked intimal proliferation in small artery (low power).



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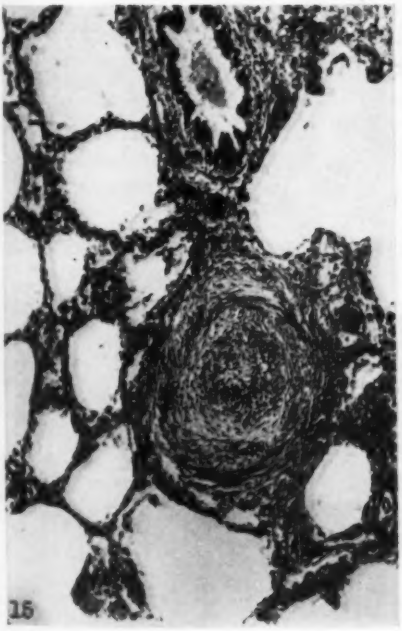

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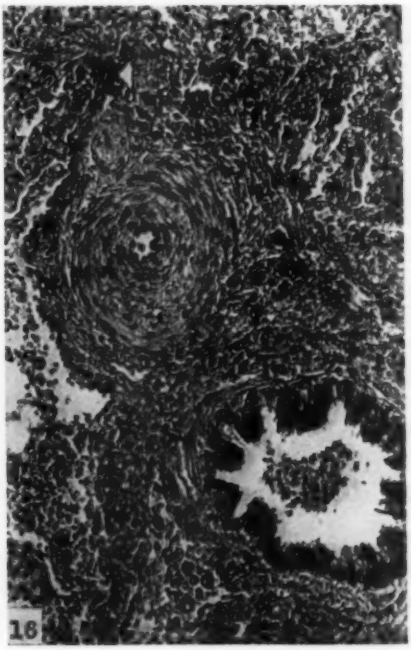

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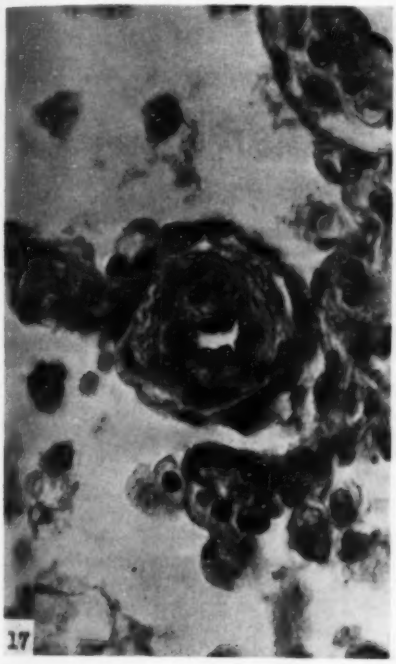
PLATE V—Case 4

FIGS. 17–19. Marked arteriolar hypertrophy and intimal proliferation in arterioles of alveolar walls (high power).

FIG. 20. Recanalized thrombus in terminal artery (high power).



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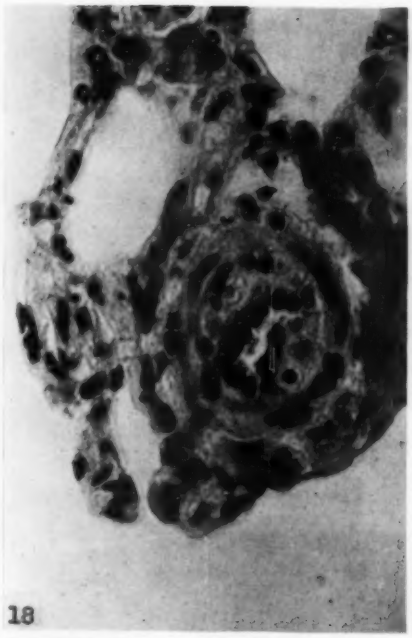

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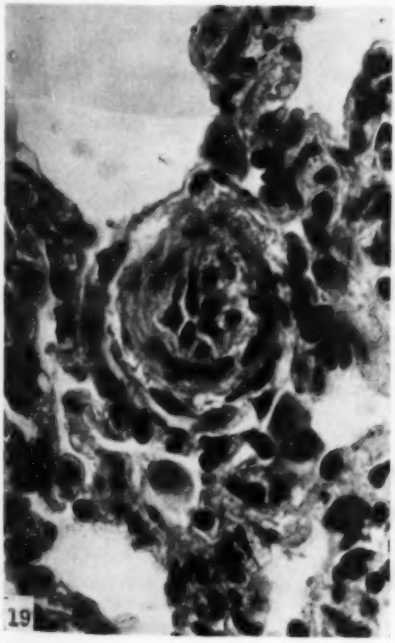

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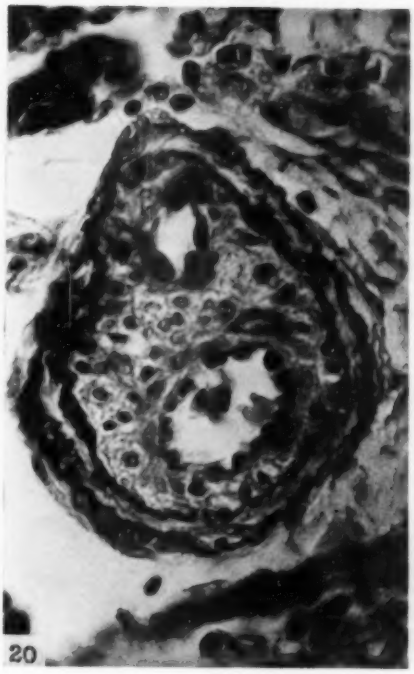

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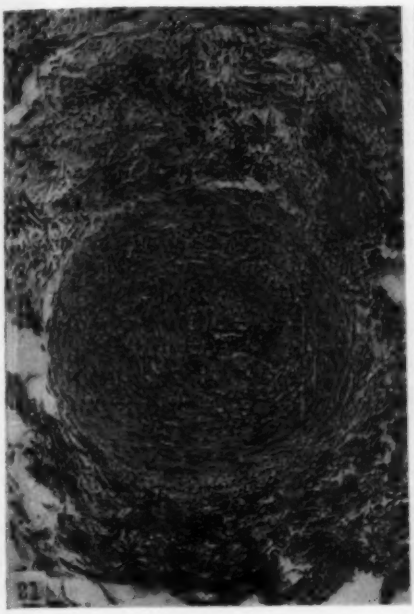
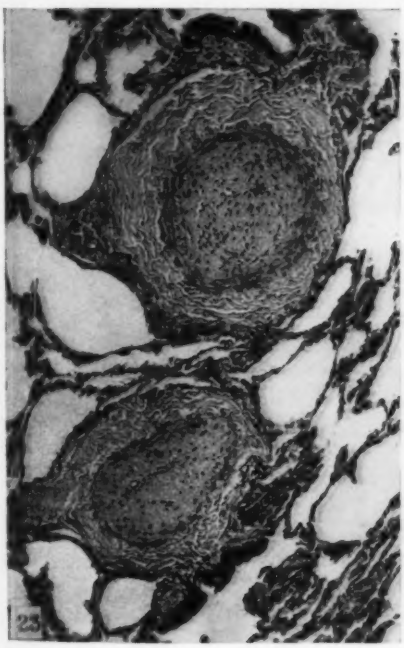
PLATE VI—Case 5

FIG. 21. Still active arteritis with healing resulting in occlusion of lumen.

FIGS. 22–23. Hyaline scar obliterating arterial lumina and media, suggestive of healed arteritis (low power).

FIG. 24. Lesion characteristic of a healed necrotizing arteritis (elastic stain; low power).





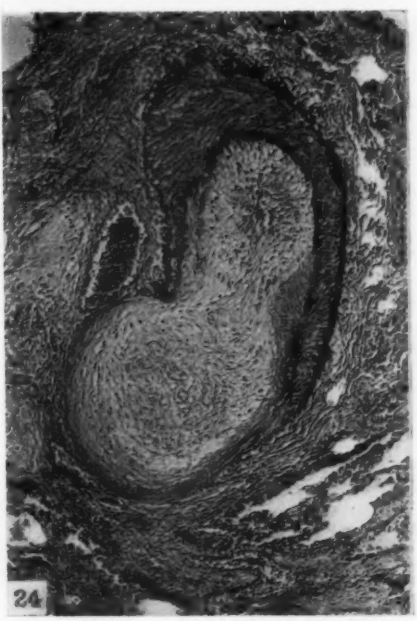


PLATE VII—Case 6

FIG. 25. Pulmonary arteriosclerosis of unexplained etiology (low power).
FIGS. 26–28. Organized recanalized thrombi simulating arteriosclerosis (low power).

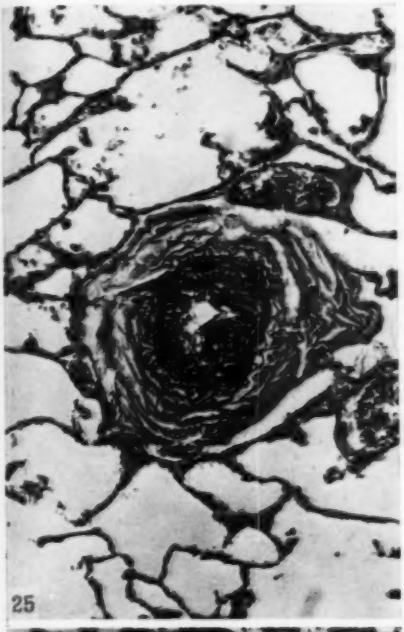

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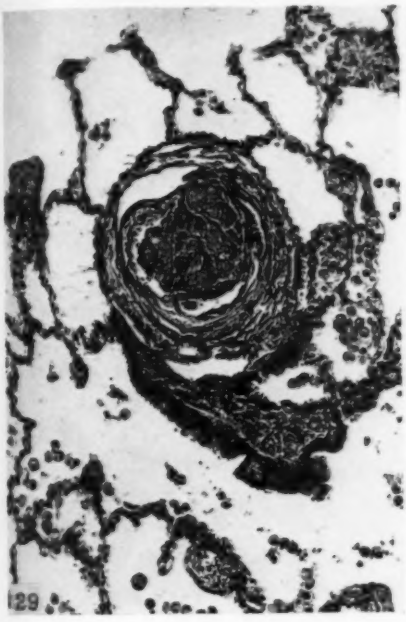
PLATE VIII—Case 7

FIG. 29 and 30. Organizing recanalizing thrombi (low power).
FIGS. 31 and 32. Pulmonary arterial hemorrhages and arteritis (low power).



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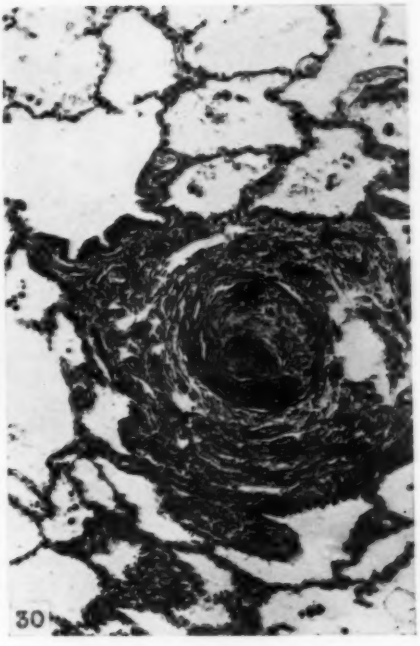

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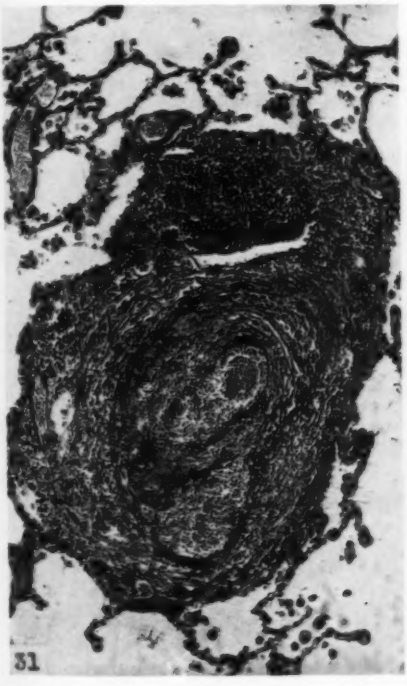

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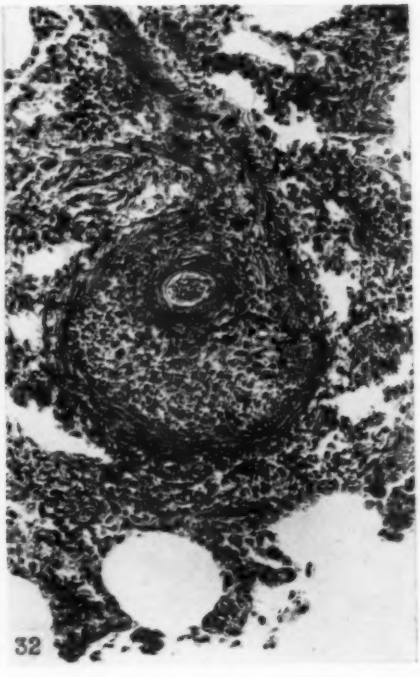

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PLATE IX—Case 7

FIG. 33. Arteritis in a small pulmonary artery with fresh necrosis of muscle in media (low power).

FIG. 34. Organized recanalized thrombus and scarring of media (low power).

FIGS. 35 and 36. Pulmonary vascular lesions probably the consequence of organized thrombi (low and high powers).

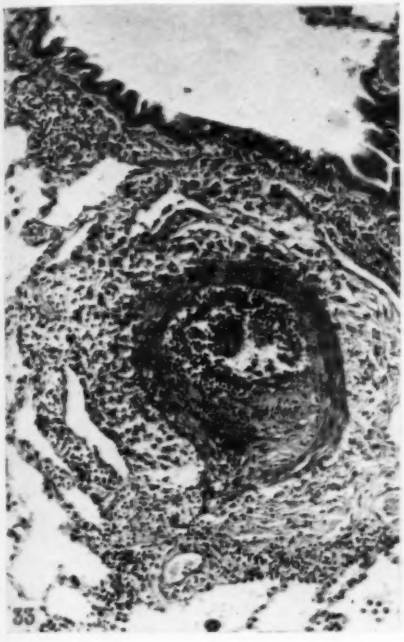
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PLATE X—Case 8

FIGS. 37 and 38. Organized recanalized thrombi in pulmonary arteries (low power). Media has been destroyed in several areas.

FIGS. 39 and 40. Pulmonary arteriosclerosis of unknown etiology (low power).

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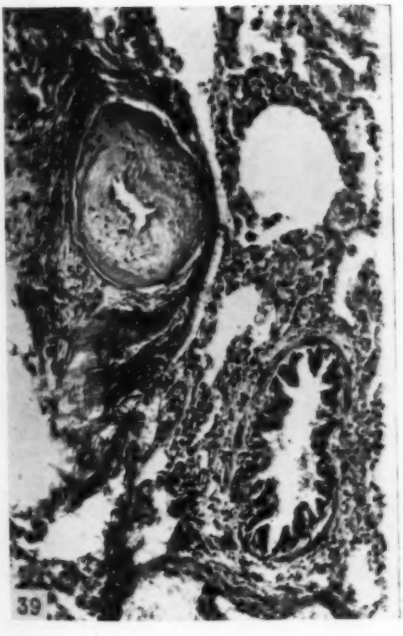
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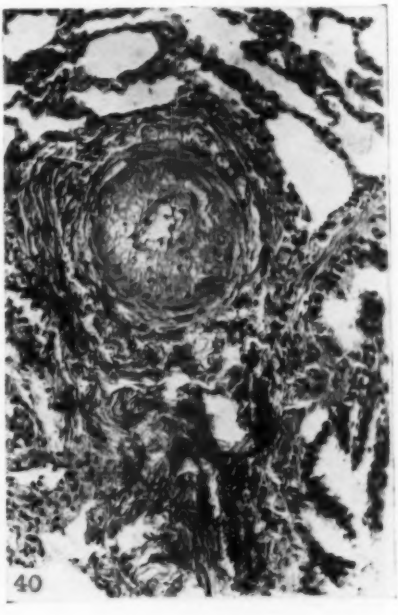
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PLATE XI—Case 9

FIGS. 41–43. Vascular lesions simulating arteriosclerosis probably a result of organized thrombi (low power).

FIG. 44. Leucocytes beneath endothelium, probably in organizing thrombus.

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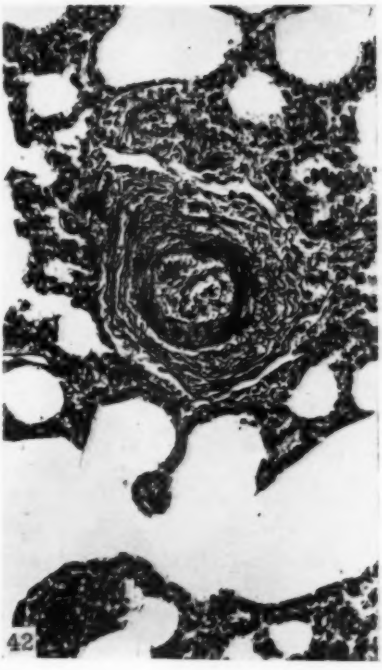
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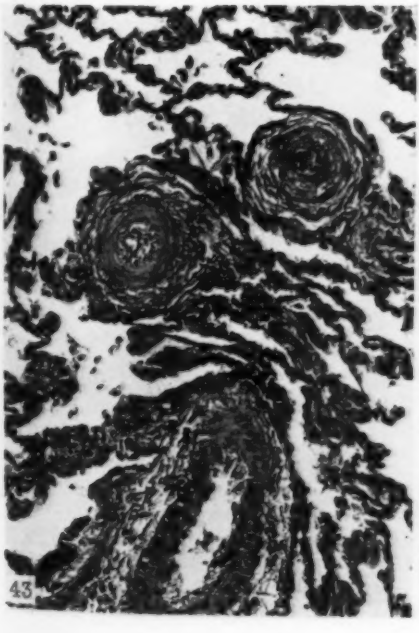
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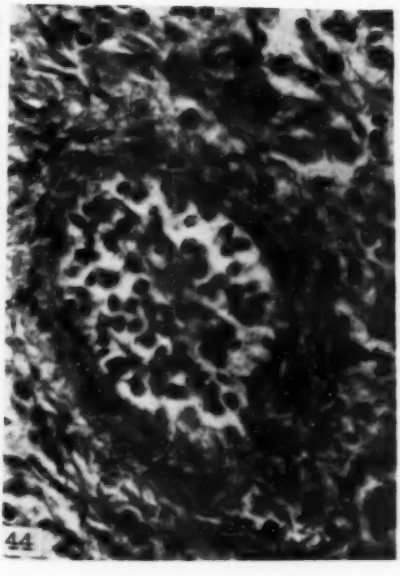
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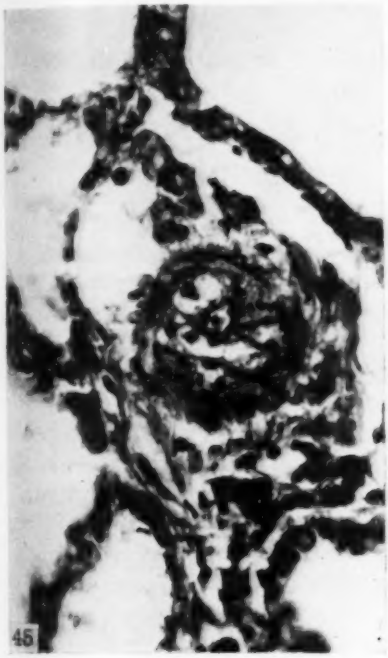
PLATE XII—Case 9

FIGS. 45 and 46. Arteriolar intimal lesions occluding the lumina and suggesting origin as thrombi (high power).

FIG. 47. Hyaline scarring of intimal tissue obliterating lumen of arteriole (high power).

FIG. 48. Arteriolar lesion with nuclear fragmentation in media and obliterative intimal plaque (high power).



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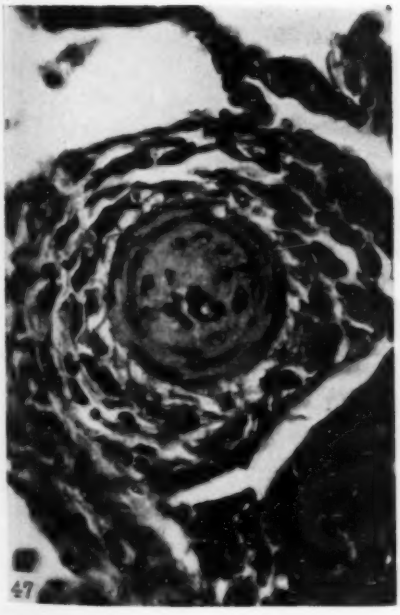

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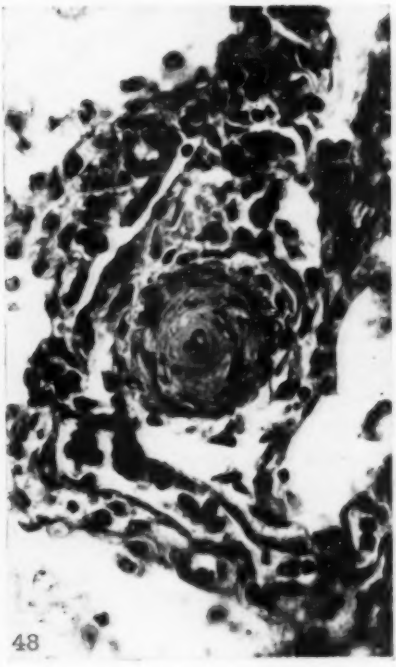

48

THE CLINICAL AND PATHOLOGIC ASPECTS OF PREMATURE PERINATAL DEATH*

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Prematurity is the major factor associated with neonatal deaths and its importance has long been emphasized. There has been much less emphasis placed upon analyzing the specific pathologic entities that play a more important role than prematurity per se. Interest in a greater understanding of these primary etiologic factors has prompted this review of the clinicopathologic problem. Very careful clinical, pathologic, endocrinologic and statistical data were correlated to effect an exacting evaluation of each individual case. It was hoped that the various factors present could be placed in their proper perspective through the use of a specific pathologic classification. A further objective was to test the practical value of a standard classification and suggest revisions as they seemed necessary. It should be emphasized at the beginning that we have been unable to establish a classification that is totally satisfactory to meet the problem in every case. Also, in a significant minority of cases the specific cause of death is completely or partially unexplained; or else so complex that the case involves multiple significant pathologic findings quite diverse in their implications.

PRESENT STUDY

The present study comprises an analysis of the premature infant deaths over a thirteen year period extending from January 1, 1937 to December 31, 1949. In this period 26,776 infants, weighing 1000 grams and over, have been delivered on the Obstetric Service of the Johns Hopkins Hospital with an overall mortality of 1,043 cases (3.8 per cent), consisting of 567 stillbirths (2.1 per cent) and 476 neonatal deaths (1.7 per cent). Of the 26,776 total infants delivered, 3,008 infants were in the 1000–2499 gram weight group, an incidence of prematurity of 11.2 per cent. Among the 3,008 premature deliveries, 566 infants died, thus giving a mortality of 18.8 per cent (Table I). Of the 23,768 infants delivered with a birth weight of 2500 or more grams, 477 died, yielding a mortality of 2.0 per cent. Although the premature group comprises only 11.2 per cent of the total number of infants, it accounts for 54 per cent of the total infant mortality.

In 1949 the definition of premature birth was altered by state law whereby

* This investigation was supported in part by a grant from the Playtex Park Research Institute.

TABLE I

Total Premature Perinatal Mortality (1000–2499 Grams) Johns Hopkins Hospital (1937–1949)

Infant Weight in Grams	Infants	Deaths	Per Cent
2000–2499	2,019	169	8.4
1500–1999	639	190	29.7
1000–1499	350	207	59.1
Total.....	3,008	566	18.8

the weight standard was lowered from 1000 grams to 400 grams without stipulation regarding a designated period of viability. In 1949, with the new definition, there was naturally a substantial increase in the number of cases classified as premature births. During 1949 at the Johns Hopkins Hospital 49 infants fell within this group (400–999 grams). When these fetuses are included in the infant mortality statistics for 1949, the group comprises 36.2

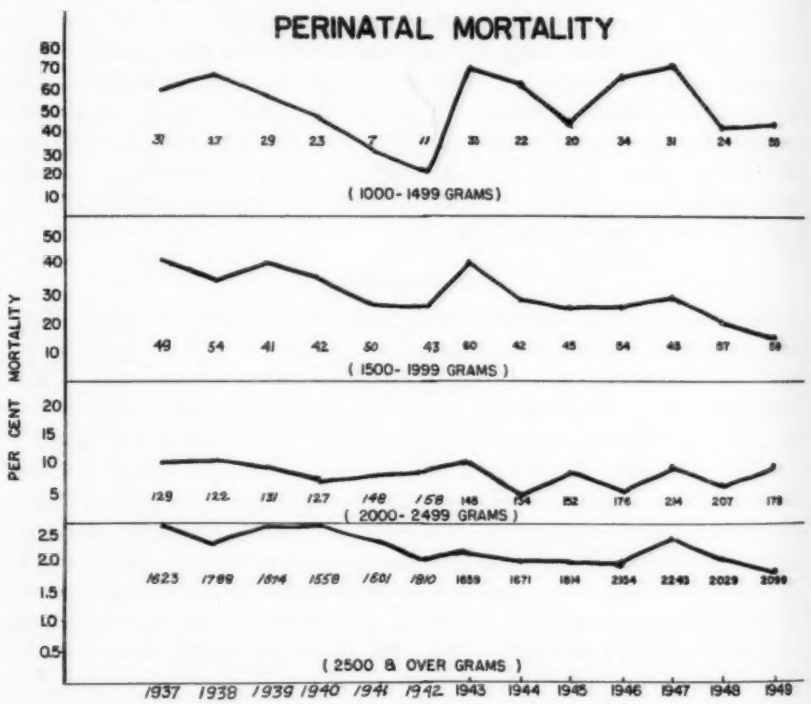

FIG. 1. Graph illustrating the perinatal mortality (over 1000 grams) in the Johns Hopkins Hospital during the period of years from 1937 to 1949. The percentage mortality is expressed in weight increments of 500 grams.

TABLE II

Perinatal Premature Mortality by Race (1000–2499 Grams), Johns Hopkins Hospital (1937–1949)

Infant Weight in Grams	White			Negro		
	Infants	Deaths	Per Cent	Infants	Deaths	Per Cent
2000–2499	826	82	9.9	1,193	87	7.3
1500–1999	254	70	27.6	385	120	31.2
1000–1499	131	76	58.0	219	131	59.8
Total	1,211	228	18.8	1,797	338	18.8

per cent of the entire fetal wastage since all but two of these fetuses succumbed. Over the 13 year period of the study 83 such infants were delivered and 76 deaths are recorded.

At this point it is proper to define the term perinatal mortality as including both fetal deaths (stillbirths) and deaths of live births (neonatal deaths). Since we have used weight in grams as a standard for viability it is also important to qualify the term perinatal mortality with the weight of the infants. Therefore, in the remainder of this discussion only the premature perinatal mortality in infants between 1000–2499 grams will be evaluated. When the total premature mortality (1000–2499 grams) is plotted according to the year by weight increments, the rates are discouragingly constant over the 13 year period of the study, (Fig. 1). There is a slight downward trend in the 1500–1999 gram group, but in general the findings point to the great need for attacking the specific causes of death once they are clearly defined.

The infant mortality and its relation to weight groups and race is illustrated in Table II. The rather striking reduction in mortality with increasing weight is clearly demonstrated. The usual overall disparity in perinatal mortality according to race was surprisingly absent in the premature group. The infants of Negro patients are usually more mature than white infants at the same weight levels, and this fact tends to equalize the mortality in the two groups.

In Table III the distribution of total neonatal deaths by weight increments

TABLE III

Distribution of Total Premature Neonatal Deaths (1000–2499 Grams) from Two American Clinics

Infant Weight in Grams	Potter and Dieckmann 1941–1946		Anderson and Nesbitt 1937–1949	
	No.	Per cent	No.	Per cent
2000–2499	27	26.2	77	24.8
1500–1999	37	35.9	109	35.1
1000–1499	39	37.8	124	40.0
Total	103	100.0	310	100.0

TABLE IV

Percentage of Perinatal Autopsies by Year and Interval Between Death and Autopsy, Johns Hopkins Hospital (1937–1949)

Premature Infants (400–2499 Grams)

Year	Per Cent Autopsies	Time of Autopsy After Delivery of Premature			
		12 hours or less	13–21 hours	22–30 hours	Over 30 hours
1937	78.85	2.28	4.56	12.19	80.97
1938	75.0	7.14	4.76	2.38	85.72
1939	76.27	6.67	4.44	4.44	84.44
1940	65.0	11.54	11.54	7.69	69.23
1941	65.51	0	0	10.53	89.47
1942	53.33	0	0	18.75	81.25
1943	46.67	3.57	10.71	7.14	78.57
1944	93.75	16.67	16.67	16.67	50.00
1945	43.24	0	0	31.25	69.75
1946	75.51	5.41	2.70	13.51	78.37
1947	96.61	8.77	7.02	31.58	52.63
1948	100.00	68.19	13.64	13.64	4.54
1949	98.95	79.79	19.15	0	1.06
Total.....	77.10	25.66	9.29	11.11	53.74

in our series has been compared with that reported from the Chicago Lying-In Hospital (19). We were interested to see that there is a striking similarity in the figures from the two clinics. In a previous study (16) we have shown that the similarity also exists between the two in the general distribution of fetal deaths in utero.

Table IV shows the yearly autopsy percentages as well as the elapsed period of time between delivery or infant death and autopsy. It can be readily seen that the effort of the authors has succeeded in obtaining more autopsies and with much less delay. In recent years there has been an autopsy rate of 98 per cent, and 80 per cent are performed in 12 hours or less. It cannot be overly emphasized that careful histologic evaluation requires fresh tissue without significant postmortem change.

Approximately fifteen blocks of tissue are prepared from each autopsy after a careful gross examination. The individual organs are weighed and the specific gravity of the lungs obtained. Routine sections are taken from the lungs, liver, bone, kidneys, adrenals, spleen, gonads, pancreas, thymus, skin, brain, heart, while other tissues are obtained as indicated. H and E stains are done routinely, and fat stains are employed on the livers of all infants showing gross evidence of anoxia. Glycogen, bacterial and Levaditi stains are done upon indication, the latter as a matter of routine in all seropositive mothers. Bacteriologic technics are employed as needed in specific cases. The brains have been retained for ultimate study in detail as a special project. Each however is carefully examined grossly and sectioned for routine staining.

PREMATURE ANTEPARTUM (BEFORE ONSET OF LABOR) STILLBIRTHS

In Table V the 566 premature deaths are grouped according to specific cause of death (77.1 per cent of cases were autopsied). In addition the total group has been subdivided into stillbirths (antepartum and intrapartum) and

TABLE V

Causes of Premature Perinatal Death (1000–2499 Grams)

Total Cases, Includes Unautopsied Cases, Johns Hopkins Hospital, 1937–1949

Cause of Death	Stillbirths				Neonatal Deaths			
	Antepartum	Intrapartum	Total no.	Per cent	Heart beat no. resp.	Respirations	Total no.	Per cent
I. Anoxia	42	45	87	34.4	5	65	70	22.4
Placenta previa	6	3	9		0	20	20	
Abruptio placenta	20	22	42		3	13	16	
Cord	2	4	6		0	4	4	
Maternal complications	6	6	12		0	9	9	
Complications of labor	4*	7	11		0	4	4	
Other	4	3	7		2	15	17	
II. No abnormal state	110	11	121	47.8	1	84	85	27.2
Without maternal disease	24	8	32		1	33	34	
With toxemia	24	3	27		0	11	11	
Maternal diabetes	2	0	2		0	1	1	
Maceration	40	0	40		0	0	0	
Unclassified	20	0	20		0	39	39	
III. Birth injury	1	6	7	2.8	3	37	40	12.8
Trauma	1	0	1		0	4	4	
Anoxic brain hemorrhage	0	6	6		3	33	36	
IV. Malformation	13	13	26	10.3	1	18	19	6.1
V. Abnormal pulmonary ventilation	0	0	0	0.0	0	58	58	18.5
VI. Infection	6	1	7	2.8	1	34	35	11.2
Syphilis	6	1	7		1	4	5	
Other	0	0	0		0	30	30	
VII. Erythroblastosis	1	0	1	0.4	0	2	2	0.6
VIII. Other conditions & causes	4	0	4	1.6	0	4	4	1.3
Total	177	76	253	100.0	11	302	313	100.0

* Antepartum fever with premature rupture of membranes.

neonatal deaths (heart beat without respiration at birth and those cases with respiration). Of the 566 deaths in the group 1000–2499 grams, 253 or 44 per cent occurred before birth; and of these 177 (31 per cent of total) occurred before the onset of labor. Despite meticulous scrutiny of these latter 177 cases, it was possible to find specific pathologic causes of death in only 37.8 per cent. Anoxia (principally abruptio placenta) was the major factor in those cases in which pathologic changes were noted (42 cases of the 177 total cases). Twenty-four cases were associated with maternal toxemia and thirteen cases of fetal death were explainable by malformations incompatible with life. There were four cases attributed to syphilis and two cases in which syphilis possibly played a role. Among the antepartum stillbirths, one fetus in the 1500–1999 gram group had a brain hemorrhage in association with a tentorial tear. The case was classified under trauma but probably the death was from other causes. Ninety cases showed no specific lesions at autopsy other than maceration (40 cases). The latter cases preclude accurate pathologic evaluation, and are categorized under "No Abnormal State". It should be pointed out that this category is heterogenous in its make up and comprises a group of fetal or neonatal deaths in which no major pathology responsible for death is noted. Fetuses without major pathologic lesions dying in association with maternal toxemia or diabetes are also placed in this category.

PREMATURE INTRAPARTUM (DURING LABOR) STILLBIRTHS

Seventy-six cases (26 per cent) of the premature stillbirth group died during labor, thus constituting 13 per cent of the total premature deaths. Specific etiologic factors responsible for death were found in 85.6 per cent of the cases. This group therefore is much more encouraging to the pathologist. The principal cause of death was again found to be anoxia (45 cases) and represented 59.2 per cent of the total deaths in this category. Abruptio placenta was responsible for the majority of deaths in the anoxia group, although cord obstruction and abnormal labors were important factors. The second largest group of deaths was associated with congenital malformations, the most important of which were brain defects. There were six infants (7.9 per cent) with intracranial hemorrhage. These cases were originally classified under trauma in order to form a group for study. An individual case evaluation has been carried out to determine evidences of stress, laceration, location of bleeding site, etc. It is interesting to note that none of the six cases in this category showed intracranial lacerations, rupture of vessels, or other evidence of trauma. We now believe this finding, namely brain petechiae, subarachnoid and intraventricular hemorrhage without lacerations, to be associated with anoxia; and the cases are so classified. These lesions in the brain are characteristically found in association with other typical findings of anoxia elsewhere in the body. More will be said concerning this point later.

The generally accepted pathologic criteria of anoxia advanced by Clifford (3) and Potter (18) are as follows:

1. Scattered petechial hemorrhage in the visceral pleura, cortex of the thymus, epicardium region of the coronary sinus and pleural surface of the diaphragm.
2. Engorgement of liver sinusoids and thymus vessels.
3. Occasional hemorrhages in the brain substance.
4. Interstitial and intra alveolar hemorrhages into the lungs.
5. Occasional subarachnoid hemorrhage.

TABLE VI

Causes of Premature Perinatal Death (1000–2499 Grams) in Autopsied Cases Only, Johns Hopkins Hospital, 1937–1949

Cause of Death	Stillbirths		Neonatal Deaths		Totals	
	No.	Per cent	No.	Per cent	No.	Per cent
I. Anoxia	65	36.5	63	24.5	128	29.4
Placenta previa	8		19		27	6.3
Abruptio placenta	32		11		43	9.8
Cord	4		3		7	1.6
Maternal complications	8		9		17	3.9
Complications of labor	6		4		10	2.3
Other	7		17		24	5.5
II. No abnormal state	78	43.8	42	16.3	120	27.6
Without maternal disease	32		29		61	14.0
With toxemia	24		11		35	8.3
Maternal diabetes	1		2		3	0.6
Unclassified	6		0		6	1.3
Maceration	15		0		15	3.4
III. Birth injury	7	3.9	39	15.2	46	10.5
Trauma	1		4		5	1.3
Anoxic brain hemorrhage	6		35		41	9.2
IV. Malformation	17	9.5	20	7.8	37	8.4
V. Abnormal pulmonary ventilation	0	0.0	57	22.2	57	13.0
VI. Infection	7	3.9	31	12.1	38	8.8
Syphilis	7		4		11	2.6
Other	0		27		27	6.2
VII. Erythroblastosis	0	0.0	2	0.8	2	0.6
VIII. Other conditions or causes	4	2.2	3	1.2	7	1.6
Total	178	100.0	257	100.0	435	100.0

6. Debris from amniotic fluid in the lungs.
7. Generalized edema of organs.

In addition to these changes, there is often fatty infiltration in the heart, kidneys, and liver. In the centers of liver lobules are fat-free sharply outlined vacuoles. Gilman and Gilman, (9) Muller and Rotter (15) have demonstrated vacuolar degeneration of the central part of liver lobules in humans in acute high altitude death. Recently Gruenwald (10) has added the observation that degenerative changes are more marked on the right half of the liver than the left half. This may be due to a peculiarity of the fetal circulation in which the arterial blood from the umbilical vein reaches only the left half of the liver and thereby protects it from the effects of anoxia.

Many of the antepartum stillborn infants were so badly macerated that autopsies were not performed, especially in the earlier years of the study. Only 70.3 per cent of the total stillborn group were autopsied. In an attempt to evaluate the specific causes of death in the autopsied cases Table VI was compiled. Causes of death however were found in only 56.2 per cent of the total cases, and again anoxia from placental complications was the principle offender. The unautopsied cases (22.9 per cent of the total) were chiefly macerated fetuses, and when excluded they did not influence the relative importance of specific causes of death.

Congenital malformations were important factors, and the most important of these were brain defects. It is always difficult to evaluate how a congenital malformation causes intrauterine death. From our data the chances of a premature infant dying of malformation are greater than that of a term infant, although the percentage of total deaths in the respective weight groups are almost the same. Support for these conclusions can be observed in the following tabulation:

Infant Weight	Infants	Malformation Deaths	Incidence: Total Births
2500 Grams +	23,768	53	1:448.4
1000–2499 Grams	3,008	46	1:65.4
Total	26,766	99	1:270.3

PREMATURE NEONATAL DEATHS

Of the 566 deaths in premature infants, 313 or 55 per cent occurred after birth. Eleven of these infants had a perceptible heart beat but at no time were seen to make respiratory efforts. Five of the eleven cases showed evidence of marked anoxia pathologically; these included three cases of intracranial hemorrhage without evidence of trauma. There were three hundred and two infant deaths in the premature group that showed respiratory movement at birth.

In the total neonatal group, the principle causes of death are associated with anoxia, accounting for 70 deaths or 22.4 per cent of the total in this category.

It is important to notice in Tables V and VI that there were 36 cases of intracranial hemorrhage unassociated with lacerations, rupture of vessels, or objective evidence of stress. There was no specific causative factor other than severe anoxia which was, in most instances, responsible for rather typical pathologic findings elsewhere in the body. It can be readily seen that anoxia has played a specific role in approximately one-third of the total neonatal deaths. All these cases have the common denominator of pathologic evidence of anoxia, but the group per se is heterogenous. In this group placental and cord complications predominate; but in addition there is a large group of unrelated maternal complications which have produced anoxic changes in the infant. These complications include toxemia, diabetes, sickle cell anemia, intrapartum fever, inertia, hyperthyroidism, etc. We are now classifying specific acute and chronic maternal diseases under a special category even though the fetus or infant shows pathologic evidence of anoxia. This has succeeded in clarifying and simplifying our classification.

The largest *single* group of neonatal deaths, however, is associated with abnormal pulmonary ventilation. Lung physiology is intimately related to the histologic degree of maturity. In the early periods of viability the alveoli are lined with cuboidal cells that separate the blood vessels from the air spaces, thereby forming a difficult barrier to the exchange of gases. The blood vessels become more numerous with maturity of the lung and a vascular network comes to lie in direct contact with the air spaces. Lung physiology is further related to specific pathologic changes in the form of resorption atelectasis, pneumonia, and hyaline like membrane. The latter finding appears as a finely granular, pink staining material condensed against the walls of the alveoli and is associated with varying degress of atelectasis and superimposed infection. The clinical course of the infant is one of increasing respiratory distress, often following a characteristically progressive course to death, after an initial variable period in which respirations are fairly normal. The etiology and pathology of this condition is complex and will be reported in a special study. Suffice to say that it does not occur in stillborn fetuses, and the condition is much more common in the premature than term infants. Multiple gestation and birth by cesarean section seem to be predisposing factors, and there is an increased incidence of hyaline like membrane in the lungs of infants of diabetic mothers.

In the present study 98 infants (1000–2499 grams) showed distinct pulmonary hyaline like membranes. Table VII shows the incidence of this lesion by weight groups in autopsied neonatal deaths, and Table VIII shows the distribution of the membrane according to the main categories of death. It can be seen that the hyaline like membrane occurs in the presence of other specific pathologic findings that undoubtedly play a role in the infant death.

TABLE VII

Weight Distribution of 98 Premature Neonatal Deaths with Pulmonary Hyaline-like Membrane, Johns Hopkins Hospital (1937–1949)

Infant Weight, Grams	Neonatal Deaths		Deaths with Hyaline Membranes	Per Cent of Neonatal Deaths	
	Total	Autopsies		Total cases	Autopsied cases
2000–2499	78	64	30	38.5	46.9
1500–1999	110	89	34	30.9	38.2
1000–1499	125	104	34	27.2	32.7
Total prematures	313	257	98	31.3	38.1

TABLE VIII

Hyaline-like Membrane Associated with Other Causes of Premature Neonatal Death (1000–2499 Grams), Johns Hopkins Hospital, 1937–1949

Cause of Death	Autopsied Cases	Per Cent	Hyaline Membrane	
			No.	Per cent
I. Anoxia	63	24.5	29	46.0
Placenta previa	19		9	
Abruptio placenta	11		5	
Cord	3		1	
Maternal complications	9		5	
Complications of labor	4		1	
Other	17		8	
II. No abnormal state	42	16.3	8	19.0
Without maternal disease	29		3	
With toxemia	11		4	
Maternal diabetes	2		1	
Unclassified	0		0	
Maceration	0		0	
III. Birth injury	39	15.2	15	38.5
IV. Malformation	20	7.8	2	10.0
V. Abnormal pulmonary ventilation	57	22.2	32	56.1
VI. Infection	31	12.1	10	32.3
Syphilis	4		0	
Other	27		10	
VII. Erythroblastosis	2	0.8	0	0.0
VIII. Other conditions or causes	3	1.2	2	66.7
Total	257	100.0	98	38.1

TABLE IX

Incidence of Hyaline-like Membranes in Cases of Premature Neonatal Death as Determined by the Presence or Absence of Other Major Pathologic Findings

Group	Number	Hyaline-like Membrane	
		Number	Per cent
A*	86	35	40.7
B†	171	63	36.8
Total	257	98	38.1

* Neonatal deaths with pulmonary pathology only and without maternal, placental or cord complications (Group A).

† Neonatal deaths with placental, cord, or maternal complications, or intrinsic infant pathology designated as specific causes of death, (Group B).

Nevertheless 40.7 per cent of the cases of hyaline like membrane appear in infants where there is no pathologic change outside the lung (Table IX). This fact has led us to the belief that the hyaline like membrane of marked degree and in association with 70 or more per cent pulmonary atelectasis is indeed a specific cause of infant death. We wish to emphasize however that the cases of abnormal pulmonary ventilation often occur in the presence of other major pathologic changes; thus necessitating a careful clinical and pathologic appraisal of each case individually to place the factors in their proper perspectives.

There is a definite inverse proportion between the length of neonatal life and the extent of hyaline like membrane found at autopsy. Infants surviving longest usually have less extensive hyaline like membranes than those dying more quickly, and have a higher incidence of associated pneumonitis. The latter finding is also correlated with maternal complications of intrapartum fever and rupture of membranes for 3–4 days prior to delivery. Atelectasis plays an important role in the physiopathologic evaluation; and it must be considered as well as infection, aspiration phenomena, and other pulmonary changes in expressing the total cases of "abnormal pulmonary ventilation". For this reason we do not classify cases according to aspiration and atelectasis per se as a specific cause of death, but relate these findings to the more general classification of anoxia and abnormal pulmonary ventilation.

As previously mentioned we attribute intracranial hemorrhage to anoxia in the absence of gross evidence of trauma. Table X shows that there were 44 cases (7.8 per cent) in the present study in which brain hemorrhage was a major cause of death. The incidence of brain hemorrhage was lowest in the premature weight group 1500–1999 grams. Careful appraisal of each case revealed that only two cases of brain hemorrhage were associated with lacerations of the falx

TABLE X

Brain Hemorrhage Premature Perinatal Mortality (1000–2499 Grams), Johns Hopkins Hospital, 1937–1949

Infant Weight in Grams	Infants	Deaths	Brain Hemorrhage Deaths	
			Number	Per cent
2000–2499	2,019	169	16	9.5
1500–1999	639	190	10	5.3
1000–1499	350	207	18	8.7
Total	3,008	566	44	7.8

or tentorium (Table XI). We concur in the general concept that vessel walls are damaged through the ischemic changes of anoxia; and petechial hemorrhages in the brain substance as well as more massive subarachnoid and intraventricular hemorrhages occur secondarily. These latter vascular changes constitute by far the commonest etiologic factor in the production of intracranial hemorrhage in the premature infant. Table XII shows that in 47 total cases of birth injury, including 44 cases of brain hemorrhage, anoxia producing maternal complications were evident in 50 or more per cent of the cases.

The incidence of intracranial injury as a cause of perinatal mortality is undoubtedly being reduced by modern obstetric practice. Older data, such as that of Ford, (8) attribute at least one-third of all deaths within the first two weeks of life to cerebral birth injury. Holland (13) found tentorial tears in 81 of 167 fetuses examined. In the present study only 4.5 per cent of premature infants dying with brain hemorrhage had tentorial tears associated with intracranial hemorrhage. D'Esopo and Marchetti (5) reported a reduction of one-half the deaths due to birth injury in the New York Lying-In and Sloane Maternity Hospitals in two groupings of their cases, 1935–1937 inclusive as compared with 1938–1940. Smith (20) reports similar reductions in the

TABLE XI

Perinatal Premature Mortality, Specific Types of Brain Hemorrhage (1000–2499 Grams), Johns Hopkins Hospital, 1937–1949

Infant Weight in Grams	Generalized Hemorrhage				Anoxia Group		
	Tentorial tear	Falx tear	Falx and tentorial tear	No tear	Ventricular and subarachnoid	Ventricular only	Total
2000–2499	0	0	1	3	8	4	16
1500–1999	1	0	0	4	4	1	10
1000 1499	0	0	0	5	8	5	18
Total	1	0	1	12	20	10	44

TABLE XII

Maternal Complications Associated with Cases of Birth Trauma and Anoxic Brain Hemorrhage, Premature Group (1000–2499 Grams), Johns Hopkins Hospital, 1937–1949

Maternal Complication	Stillbirth				Neonatal			
	Before labor	During labor	Total	Per cent	Without resp.	With resp.	Total	Per cent
None	0	4	4	57.1	2	18	20	50.0
Placenta previa	0	0	0	0.0	0	4	4	10.0
Abruptio placenta	0	0	0	0.0	1	5	6	15.0
Bodily violence	1	0	1	14.3	0	0	0	0.0
Prolapse of cord	0	1	1	14.3	0	4	4	10.0
Uterine rupture before labor	0	0	0	0.0	0	0	0	0.0
Uterine rupture during labor	0	0	0	0.0	0	0	0	0.0
Dystocia	0	0	0	0.0	0	0	0	0.0
Inertia	0	0	0	0.0	0	3	3	7.5
Abnormal uterine contractions	0	0	0	0.0	0	0	0	0.0
Intrapartum fever	0	0	0	0.0	0	0	0	0.0
Hydramnios	0	0	0	0.0	0	1	1	2.5
Anesthesia accident	0	0	0	0.0	0	0	0	0.0
Cerebral accident	0	1	1	14.3	0	0	0	0.0
Other	0	0	0	0.0	0	2	2	5.0
Total	1	6	7	100.0	3	37	40	100.0

per cent of premature and full term stillbirths and neonatal deaths in the Boston Lying-In Hospital due to gross intracranial hemorrhage during the years 1931–1935 as compared to 1941–1945. However, an increase in asphyxial hemorrhages occurred during a 15 year period in which the overall mortality was decreasing. Table XIII shows a similar trend in the Johns Hopkins

TABLE XIII

Comparison of Two Five-Year Periods as to Cause of Premature Perinatal Deaths (1000–2499 Grams), Johns Hopkins Hospital

Cause	1937–1941 Total Deaths		1945–1949 Total Deaths	
	No.	Per cent	No.	Per cent
I. Anoxia	73	29.9	58	24.7
II. No abnormal state	96	37.6	87	36.1
III. Birth injury (includes anoxic brain hemorrhage)	16	6.4	28	11.8
IV. Malformation	16	6.4	21	8.8
V. Abnormal pulmonary ventilation	24	9.6	23	9.7
VI. Infection	24	9.6	13	5.5
VII. Erythroblastosis	0	0.0	1	0.4
VIII. Other conditions and causes	1	0.4	7	3.0
Total	250	100·0	238	100.0

Hospital over two five year periods. The increase in the general category of birth trauma is due to a near two fold increase in anoxic brain hemorrhage (Fig. 2 and 3A–E).

Potter (17), Gruenwald (11), and others have felt that trauma plays no essential part in the causation of subependymal hemorrhage (Fig. 3-B), and that anoxia, with its congestion, causes not only subependymal, but subarachnoid hemorrhages (Fig. 3-E) as well. Gruenwald studied the veins of the subependymal area in comparison with veins of the differentiated white matter and found the former, although larger, to have thinner walls than the latter structures. Intraventricular hemorrhage may be due to anoxia and bleeding from the choroid plexus (Fig. 3-C) or vena terminalis in the wall of the lateral ventricles. Hemsath (12), in a series of brain hemorrhages, found only 15.7 per cent of the intraventricular type to be associated with tears of the dura. Ehrenfest (7) states however that the differential diagnosis of "asphyxial" hemorrhage and intracranial injury hemorrhage is difficult, since an engorged

FIG. 2. Photograph of the brain, heart, and lungs of a premature infant (1200 grams) delivered spontaneously. The infant died after 24 hours of life. Note the massive anoxic intraventricular hemorrhage forming a cast of the ventricles of the brain. The heart is pale and anemic.

FIG. 3-A. Photograph of the coronal sections of the brain of a 1050 gram live born infant which lived 16 hours, delivered of mother with vaginal bleeding during pregnancy and labor.

FIG. 3-B. Higher magnification of the ventricles of the brain shown in 3-A with marked hemorrhage in the subependymal areas surrounding the terminal vein.

FIG. 3-C. Photomicrograph of the choroid plexus described in Fig. 3-B illustrates the marked engorgment of the thin walled veins of this structure.

FIG. 3-D. Inferior surface of the brain of Fig. 2 showing massive hemorrhage about the medulla and spinal cord.

FIG. 3-E. Photomicrograph showing the subarachnoid type of hemorrhage which accumulates around the base of the brain after leakage from the ventricular system.

vein or sinus is more likely to be ruptured by an external force. He concluded that it is safer to regard every newborn infant not properly breathing as one likely to have been traumatized by birth. It should be emphasized however that these infants in poor condition at birth can be further traumatised by over zealous attempts at resuscitation (Fig. 4).

Irving (14), Potter (18), Clifford (3), and others have demonstrated the incidence of brain hemorrhage in relation to the method of delivery. Potter and Clifford find that version, breech extraction, and cesarean section are the commonest methods of delivery in the high mortality groups. It should be pointed out that a more liberal use of cesarean section in the treatment of anoxia producing placental complications could very well merely change the order of causative factors in infant death from anoxia and brain hemorrhage to the abnormal pulmonary ventilation group.

TOTAL PREMATURE NEONATAL DEATHS AND STILLBIRTHS (1000–2499 GRAMS)

Probably more important than the pathologic findings in the dead premature infant are the factors responsible for the production of premature labor. The causes of premature labor must be paramount in any analysis of premature deaths. Eastman (6), in a study of 3,331 premature infants in the Johns Hopkins

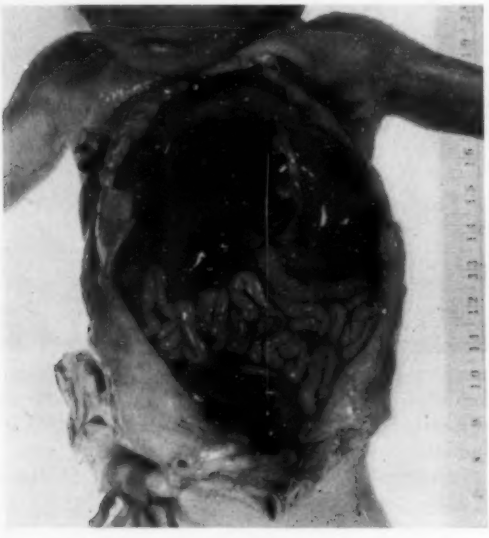

FIG. 4. An example of subcapsular hematomata of the liver due to traumatic jack knife resuscitation procedures. The cause of death in this case however was due to anoxia associated with abruptio placenta.

Hospital delivered during the period 1926–1945, summarized the known causative factors as follows:

Maternal disease, spontaneous onset	10.3%
Maternal disease, operative termination	14.3%
Congenital abnormality	1.6%
Multiple pregnancy	11.9%
Total	38.1%

The diseases most frequently responsible for the premature onset of labor were chronic hypertension, abruptio placenta, placenta previa, heart disease,

TABLE XIV

Causes of Premature Perinatal Death by Weight Groups, Johns Hopkins Hospital (1937–1949)

Cause of Death	Weight in Grams			Total	Per cent
	1000–1499	1500–1999	2000–2499		
I. Anoxia	57	58	42	157	27.7
Placenta previa	11	16	2	29	
Abruptio placenta	19	21	18	58	
Cord	5	3	2	10	
Maternal complications	3	9	9	21	
Complications of labor	10	4	1	15	
Other	9	5	10	24	
II. No abnormal state	83	63	60	206	36.4
Without maternal disease	37	9	20	66	
With toxemia	17	10	11	38	
Maternal diabetes	2	1	0	3	
Unclassified	17	28	14	59	
Maceration	10	15	15	40	
III. Birth injury	19	11	17	47	8.3
Trauma	1	2	2	5	
Anoxic brain hemorrhage	18	9	15	42	
IV. Malformation	13	15	17	45	8.0
V. Abnormal pulmonary ventilation	22	20	16	58	10.2
VI. Infection	9	20	13	42	7.4
Syphilis	4	4	4	12	
Other	5	16	9	30	
VII. Erythroblastosis	2	0	1	3	0.5
VIII. Other conditions or causes	2	3	3	8	1.4
Totals	207	190	169	566	100.0

eclampsia, and syphilis. Potter (17), in a study of 265 non-surviving live born premature infants delivered at the Chicago Lying-In Hospital between 1939 and 1945, found 56.6 per cent of the mothers had some complication of pregnancy. Among these were the following:

Toxemia	10.0%
Placenta previa	10.0%
Premature separation of the placenta	7.0%

Age of the mother, parity, and poor past obstetric history were outstanding maternal factors associated with premature deaths in Potter's study. Many studies, including that of Eastman (6), have demonstrated that premature onset of labor occurs more commonly in lower economic groups and may be associated with dietary deficiencies. No final proof for these statements is available.

The major causes of premature perinatal death according to weight groups is shown in Table XIV. Placental complications were the principle causes of death and the general anoxia group was largest of the known causes. It must be pointed out however that no abnormal state was found in 206 of 566 cases (36.4%). When all unautopsied cases are excluded, 27.6 per cent of the cases fall into the group of no abnormal state and anoxia assumes the primary role of all causes of death (Table XV). Selected causes of premature death have been listed in descending order of importance in Table XVI. The major factors in total premature perinatal death are: cause unknown, placental complications, abnormal pulmonary ventilation, toxemia, birth injury, malformation, and infection in that order. Study of the autopsied cases only, did not change the relative order of importance of the various factors associated with premature death.

TABLE XV

Causes of Premature Perinatal Death (1000–2499 Grams), Johns Hopkins Hospital, 1937–1949

Cause of Death	Total Cases		Autopsied Cases Only	
	Number	Per cent	Number	Per cent
I. Anoxia	157	27.7	128	29.4
II. No abnormal state	206	36.4	120	27.6
III. Birth injury	47	8.3	46	10.5
IV. Malformation	45	8.0	37	8.4
V. Abnormal pulmonary ventilation	58	10.2	57	13.0
VI. Infection	42	7.4	38	8.8
VII. Erythroblastosis	3	0.5	2	0.6
VIII. Other conditions or causes	8	1.4	7	1.6
Total	566	100.0	435	100.0

TABLE XVI

Selected Causes of Premature Perinatal Death (1000–2499 Grams), Johns Hopkins Hospital, 1937–1949

Cause of Death	Total Cases, Per Cent	Autopsy Cases Only, Per Cent
1. Cause unknown	29.1	18.7
Without maternal disease	11.7	14.0
Maceration only	7.0	3.4
Unclassified	10.4	1.3
2. Placental complications	15.4	16.1
Abruptio placenta	10.3	9.8
Placenta previa	5.1	6.3
3. Abnormal pulmonary ventilation	10.2	13.0
4. Toxemia	10.0	11.6
Unknown with toxemia	6.7	8.2
Toxemia with anoxia	3.3	3.4
5. Birth injury	8.3	10.5
Trauma	0.9	1.2
Anoxic brain hemorrhage	7.4	9.3
6. Malformation	8.0	8.4
7. Infection	7.4	8.8
Syphilis	2.1	2.6
Other	5.3	6.2
8. Other anoxia, conditions or causes	5.7	7.1
9. Complications of labor	2.6	2.3
10. Cord complications	1.8	1.6
11. Erythroblastosis	0.5	0.6
12. Maternal diabetes	0.5	0.6
13. Maternal complications (excludes diabetes, toxemia)	0.4	0.5
Total	100.0	100.0

Adrenal hemorrhage unrelated to trauma or anoxia has been suggested as a factor in neonatal death. We have found in our data a rather inconsequential incidence of adrenal hemorrhage by infant weight when the factors of anoxia and trauma are removed. At this stage in our knowledge we are inclined to place little emphasis on this entity as a cause of perinatal mortality.

Although the premature group comprises only 11.2 per cent of the total number of infants, it accounts for 54 per cent of the total infant mortality.

TABLE XVII

Pathologic Lesions Present in Fetuses and Infants Weighing from 400–999 Grams

Cause	Chicago Lying-In			Johns Hopkins Hospital			Total Both Studies
	Stillbirths	Neonatal deaths	Total	Stillbirths	Neonatal deaths	Total	
Anoxia							
Placenta	4	0	4	3	9	12	16
Cord	3	0	3	1	3	4	7
Other	0	0	0	0	4	4	4
Trauma*	1	5	6	0	13	13	19
Pneumonia	9	5	5	2	4	6	11
Malformation	7	1	8	0	0	0	8
Erythroblastosis fetalis	3	1	4	0	0	0	4
Maternal toxemia	5	0	5	0	6	6	11
No abnormalities	39	46	85	4	18	22	107
No autopsy	2	7	9	0	4	4	13
Pulmonary pathology	0	0	0	0	5	5	5
Total	64	65	129	10	66	76	205

* Our group includes anoxic brain hemorrhage.

Solution of the problem resides in the prevention of premature labor rather than management obstetrically or pediatrically after it has occurred. Advancement in the science of muscle chemistry and physiology appears to be the principal hope in the ultimate solution of this problem. We are convinced that one of the most fundamental points in the problem of prematurity is a basic understanding of the contractile system of the smooth muscle cell. Csapo (4) has evaluated muscle protein actomyocin and its enzyme systems in smooth muscle, both in experimental animals and humans under varying conditions. This work is only in its basic phase but offers hope for the better understanding of abortion, inertia, uterine atony, and the onset of premature labor.

Finally it should be emphasized that anoxic conditions in premature infants may produce sublethal brain injuries that frequently arouse greater anguish and tragedy than death itself. The obstetrician is in a strategic position to examine the possibility of cerebral damage in the new born infant. All future obstetricians must concern themselves as much with infant morbidity with its permanent effects upon the infant as with the general problem of perinatal mortality.

IMMATURE PERINATAL DEATHS (400–999 GRAMS)

In the present study 76 cases were subjected to the same clinicopathologic evaluation that was used for the other groups of premature infants. We were interested to find that the immature deaths fall into the same general categories of classification. Table XVII enumerates the findings noted and points to the

importance of anoxia as a cause of death. There are however a larger percentage of cases unexplainable by the methods of evaluation. Arey and Dent (1, 2) report intraventricular hemorrhage as the leading cause of death in this group. We have interpreted these findings as related to anoxia; but when evaluated as a separate entity, the cases comprise a group that is 17.1 per cent of the total. Potter reports that anoxia and malformations are important findings in her group. We have found that the total deaths associated with maternal toxemia take on a more important role when the immature deaths are included in the total premature group, but the other principle etiologic factors maintain their same relative significance.

SUMMARY AND CONCLUSIONS

During the period January 1, 1937 to December 31, 1949 there were 3008 premature infants (1000–2499 grams) delivered on the Obstetrical Service of the Johns Hopkins Hospital, an incidence of prematurity of 11.2 per cent. Among the 3,008 premature deliveries, 566 infants died, thus giving a mortality of 18.8 per cent. Although the premature infants comprise only 11.2 per cent of the total number of infants delivered (26,776), they account for 54 per cent of the total perinatal mortality. Over the 13 year period of the study there were 83 deliveries in the 400–999 gram group; 76 of these infants died (91.6 per cent). However, in this study our attention was directed primarily to the group of infants weighing 1000–2499 grams. A careful clinicopathologic study was carried out in this premature group to determine the pathologic changes and wherever possible the specific cause of death. To effect this end, a strict clinical and pathologic classification similar to that of Potter was employed. Perinatal mortality was defined as including both fetal deaths (stillbirths) and death of live births (neontal deaths) within specific weight groups (1000–2499 grams). For the purpose of discussion our cases were further analyzed according to the time of death; namely, fetal deaths in utero before the onset of labor, fetal deaths in utero during labor, and neonatal deaths during the first twenty-eight days of life. The latter group includes infants with heart beat and no respirations.

Of the known causes anoxia played the dominant role in the causation of premature fetal death in utero, and maternal, placental, and labor complications were the most significant sub groups in this category. The assignment of a specific cause of death was possible in a higher percentage of cases in the fetuses dying during labor, however the same etiologic factors were found to operate. Despite meticulous scrutiny of each case of fetal death in utero before the onset of labor, it was possible to find specific pathologic causes of death in only 37.8 per cent. In the group of fetal deaths dying during labor specific pathologic factors responsible for death were found in 85.6 per cent of the cases.

The second largest group of deaths was associated with congenital malformations, the most important of which were brain defects.

In the total neonatal group the principle cause of death is associated with anoxia, accounting for 70 deaths or 22.4 per cent of the total. In addition, there were 36 cases of intracranial hemorrhage associated with anoxia without demonstrable dural laceration. It can be seen that anoxia has played a specific role in approximately one-third of the total neonatal deaths—all of these cases have the common denominator of pathologic evidence of anoxia, but the group per se is heterogenous. The largest *single* entity associated with neonatal death in premature infants is abnormal pulmonary ventilation. Nearly one-half of the cases of hyaline like membrane appear in infants with no pathologic changes outside the lung. This has led us to the belief that the membrane in marked degree and in association with 70 or more per cent pulmonary atelectasis is indeed a specific cause of infant death. Infants surviving longest usually have less extensive membrane and a higher incidence of associated pneumonitis.

There were 44 cases (7.8 per cent) in the present study in which brain hemorrhage was a major cause of death. Careful appraisal of each case revealed that only two cases of brain hemorrhage were associated with lacerations of the dura. Anoxic vascular changes constitute by far the commonest etiologic factor in the production of intracranial hemorrhage in the premature infant.

In the present study the major factors in total premature perinatal death in descending order of importance are: cause unknown, placental complications, abnormal pulmonary ventilation, toxemia, birth injury (including anoxic brain hemorrhage), malformation, and infection. Study of autopsied cases only did not change the relative order of importance of the various factors associated with premature death.

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MUSICAL MURMURS

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Musical murmurs are among the most impressive of auscultatory findings, mainly because they stand in such striking contrast to the non-musical noises with which the stethoscopist is usually concerned. Much mystery has surrounded this category of cardiovascular sound. The availability of a new investigative tool prompted study of the classification, clinical significance and anatomical-hemodynamic mechanisms of these murmurs.

Several previous publications (1, 2, 3) from this laboratory have described the adaptation of the method of sound spectrography devised at the Bell Telephone Laboratories and its application to the study of cardiovascular sound. Spectral phonocardiography was the designation proposed for the method in this application since the displays differ from those of conventional oscillographic phonocardiography mainly in that frequency spectrum is displayed as well as intensity and timing. From the first it was pointed out that since this method provides a detailed time-frequency-intensity plot, it does display quality or timbre, which previously has defied precise definition in physical terms and exact representation on the printed page. The musical murmurs afford an ideal demonstration of the competence of the method in the physical description of quality. Furthermore, the spectral phonocardiogram provides a point of departure for studies of the anatomical and hemodynamic basis of variation in the quality of cardiovascular sounds.

METHODS

Methodological details have been presented elsewhere (2, 3) and will not be repeated here. Initial recordings of the heart sounds and of other physiological phenomena used for correlative purposes have been made on magnetic tape, the latter group by means of frequency modulated carriers. Appropriate sections have then been selected for spectral analysis. Some of the analyses have been made on electrosensitive paper by the earlier method and others, when improved intensity display was necessary to demonstrate better the musicality, on photographic paper by the newer method.

The Photographic Method: The marking unit of the photographic unit is a modified light modulator (Sylvania glow modulator tube R-1130B). Paper (Kodak Linograph 679) with a high degree of contrast has been used. The physical structure of the photographic display

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unit has been superimposed on the direct-writing unit and enclosed in a light-tight box which is entered via light-tight sleeves. The drum of the photographic unit is mounted on the same axis as the drum of the regular (direct-writing) unit (2) and both photographic and direct-written records can be made on the same segment of sound. A comparison of the two types of recordings has been presented elsewhere (3). See Figs. 5, 12, and 18 for other photographic records.

MUSICAL MURMURS: A DEFINITION IN PHYSICAL TERMS

Except in the most full-blown instance there is likely to be disagreement as to whether a given murmur is musical. It is clear from spectrographic studies, of which many examples are provided here, that murmurs are in general of two types: musical murmurs and noisy murmurs. Furthermore the distinction between the two is a function of the presence or absence of harmonic pattern. In predominantly musical murmurs virtually all of the sound is represented by a fundamental (first harmonic) and higher harmonics at frequencies which are multiples of that of the fundamental. Some murmurs are made up of a combination of musical components and non-musical wide band noise. In some of these instances (see below) it may be accurate to relate the musical component to the regular vibrations of an elastic structure (such as the lip of a retroverted cusp or the fibrous diaphragm of a stenotic aortic valve) and the noisy component to the turbulence set up in the blood in the vicinity of the valve orifice.

A CLASSIFICATION OF MUSICAL MURMURS

Musical murmurs of the following varieties will be discussed and demonstrated:

A. Musical diastolic murmurs.
   1. Due to aortic valve "rupture", retroversion, tear, fenestration.
   2. Due to dissecting aneurysm of the ascending aorta.
   3. Extracardiac.

B. Musical systolic murmurs.
   1. Extracardiac.
      a. Cardiorespiratory
      b. Pericardial
   2. With aortic stenosis.
   3. With mitral regurgitation.
      a. In acute rheumatic fever
      b. With bacterial endocarditis of the mitral valve
      c. In chronic rheumatic heart disease
      d. In Marfan's disease
      e. In idiopathic myocarditis, and so on

4. With ball-valve thrombus or myxoma of the atrium.
5. In pulmonary area in rheumatic heart disease.
6. With aberrant tendon of ventricle.
7. With inter-ventricular septal defect and aberrant tricuspid chordae tendineae.

C. Musical peripheral vascular murmurs.

1. Uterine souffle.
2. Cruveilhier-Baumgarten murmur.

MUSICAL AORTIC DIASTOLIC MURMURS

This important category of musical sound will be discussed under the following headings:

1) Etiology, including anatomical factors in their genesis.
2) Description of spectral phonocardiographic characteristics.
3) Hemodynamic factors in their genesis.

FIG. 1A

FIG. 1. The usual anatomical basis for musical aortic diastolic murmurs. Syphilis is the usual cause. Note the changes in the aortic intima and in the right anterior coronary cusp, the one usually affected. A. Patient W. H. (case 1). B. Drawing from another case.

4) Factors of selective transmission and resonant absorption in the quality of these murmurs at the several areas.
5) A bizarre variety of late diastolic aortic murmur with dissecting aneurysm of the ascending aorta.

Etiology: These are the murmurs variously described by analogy to the sawing of wood, the sound of a cuckoo clock, the cooing of a dove, the cry of a sea-gull, the humming of a musical top, and so on. A sea-gull murmur usually brings "ruptured aortic cusp" immediately to the mind of the clinician. However, as was demonstrated by Hodgkin, who in 1827 (4) probably described this murmur for the first time, the usual anatomical basis is retroversion of an aortic cusp (see Fig. 1). The right anterior coronary cusp is most frequently involved and syphilis is the usual cause (5). Bellet (7) presented evidence which seems to support the suggestion that destruction of the elastica which sweeps

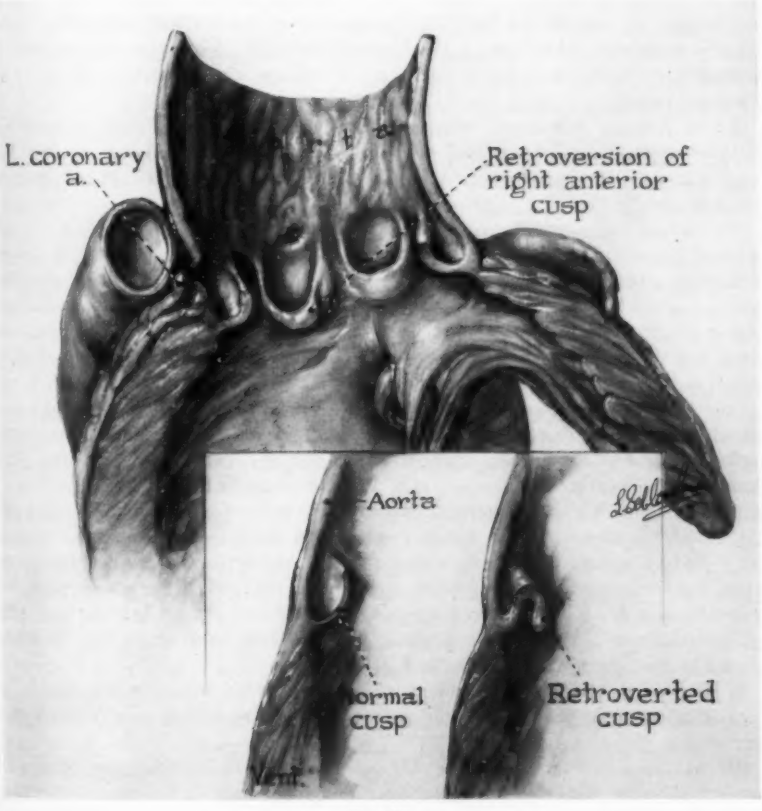

FIG. 1B

up onto the ventricular aspect of the aortic cusp from the ventricular endocardium may be the determining factor in the development of retroversion of syphilitic origin. This is one instance in which the quality of a murmur provides strong presumptive evidence of its etiology. Subacute bacterial endocarditis, rheumatic aortic valvulitis, and Marfan's syndrome (6) are also occasional causes. Traumatic rupture of a normal valve may be the basis on rare occasion; however, in such instances one must always be suspicious of pre-existing valvular disease.

The following two cases will serve to illustrate some of the clinical features presented by these patients. The first illustrates particularly well the usual etiological and anatomical findings.

Case 1: W. H. (J.H.H. 560600), a 50 year old Negro male, was admitted to the hospital because of mild pulmonary edema. Syphilis and treatment for same were denied. Six weeks before admission the patient was first seen in the Emergency Department because of pulmonary edema. At that time a loud diastolic murmur of non-musical quality was present. Blood pressure was 150/40 mm. Hg. When next seen and admitted to the hospital blood pressure was 130/30/0 mm. Hg and the diastolic murmur was now the typical loud cooing or sea-gull sound.

X-rays revealed pronounced enlargement of the left ventricle without evident aortic dilatation. Serologic tests for syphilis were positive and the spinal fluid complement fixation reaction for syphilis was also positive. Numerous blood cultures were sterile and the patient remained afebrile.

The patient demonstrated progressively more severe manifestations of congestive failure and died 19 months after appearance of the sea-gull murmur. Autopsy revealed retroversion of the right anterior coronary cusp of the aortic valve and relatively little change in the other cusps (see Fig. 1A). The sinus of Valsalva corresponding to this cusp was considerably dilated as were the other sinuses to a lesser extent. The commissures were slightly separated, and the coronary ostia somewhat high but normally patent. Mild intimal changes typical of luetic aortitis were present throughout the thoracic aorta.

Case 2: Although autopsy examination is not available to complete the evidence, the following patient was studied with such care over a period of 20 years that the evidence for non-luetic retroversion, tear, or perforation of an aortic cusp is convincing. As in this patient, abrupt onset of awareness by the patient of a musical sound in the chest occurred in a number of the patients with retroversion of an aortic cusp on the basis of syphilis. In one (T. S., J.H.H. 103485) there was good documentation of the previous existence of a non-musical aortic diastolic murmur. It is likely that retroversion of the diseased cusp occurred acutely at the time the patient became aware of the sound. One may observe two phenomena: 1) development of a musical murmur against the background of a pre-existing conventional aortic diastolic, or 2) the disappearance of the musical component of the murmur with the passage of time (see below, recording in Fig. 2).

M. G. (J.H.H. 124569), a Negro female, was 54 years old when her sixth admission to the hospital was prompted by the development of a "purring sound" in her chest four days previously.

She had been well for most of her life and previous hospital admissions were for obstetrical deliveries. Repeated serological tests for syphilis were always negative, there were never previous manifestations interpretable as syphilitic in etiology, and no therapy for syphilis had ever been given.

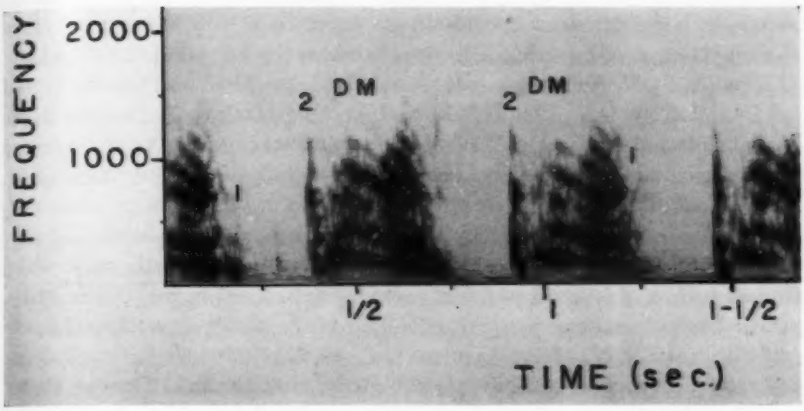

FIG. 2. Typical musical aortic diastolic murmur in patient with syphilitic aortitis. Note intensification of murmur without rise in frequency, toward end of diastole (discussed later). Three years later only a conventional noisy aortic diastolic murmur was present.

In 1938 (at the age of 40 years) during her last pregnancy, the blood pressure was 160/110 mm. Hg and cardiomegaly with signs of mild congestive heart failure was present. Tubal ligation was performed. Two years before final admission chest x-ray revealed slight enlargement to the left and there was left axis deviation by electrocardiogram. The blood pressure on repeated examinations during this period was always normal or only slightly elevated. No diastolic murmur was ever heard.

One week before admission she was awakened with a sensation of fullness in the substernal area accompanied by nausea. These symptoms passed off quickly and the patient felt well until four days before admission when, while sitting and reading the paper after supper, she suddenly became aware of a "purring and thumping" in her chest. There were no other symptoms.

On examination the blood pressure was found to be 125/65 mm. Hg in both arms. The patient was moderately obese. She was perfectly comfortable. A prominent diastolic thrill was palpable over the entire precordium. The heart was enlarged to the left. Auscultation was dominated by a very loud, cooing murmur which was maximal at the left sternal border but also audible over the skull and sacrum.

Electrocardiogram revealed the pattern of left axis deviation and left ventricular strain. By x-ray the aorta was dilated and tortuous and the innominate artery was kinked and dilated. Serologic tests for syphilis including a treponemal immobilization test were negative. The temperature was always normal and four blood cultures were sterile. See phonocardiogram in Fig. 7.

Although no signs of congestive failure were present, prophylactic digitalization was performed. However, because of the appearance of numerous ventricular extrasystoles digitalis was discontinued.

The patient did not return for further observation. She had several admissions to another hospital for treatment of congestive heart failure. She died at home 21 months after her first hospital admission.

Arteriosclerosis is by exclusion of syphilis, bacterial endocarditis, and trauma a likely cause of the aortic valve rupture in this case. Caution must always be

exercised, however, since arteriosclerosis must be a very uncommon cause. Carroll (21) could find only one patient in whom this appeared to be the basis. This patient, a Negro laborer, was seen at the Johns Hopkins Hospital in 1901 by Drs. William Osler, Rufus Cole and Thomas McCrae. He had an aortic diastolic murmur which Dr. McCrae compared to the bass string of a cello and which was audible 6 inches from the body. The autopsy was performed by Dr. W. G. MacCallum who rendered a final diagnosis of rupture of an aortic cusp due to arteriosclerosis. (It was recorded: "In connection with the musical murmur it is of interest to note the finding of a cusp of the aortic valve which flapped back and forward and was probably the causal factor".) The pathological diagnosis must be interpreted in light of the history of our knowledge of syphilitic aortitis. MacCallum himself (20) describes this well: "It was impressive, and a revelation, to listen in 1903, at the meeting of the German Pathological Society, to the discussion by Chiari and others, of the discovery by Doehle and Heller of the syphilitic nature of these changes, and particularly to realize the perfectly characteristic and peculiar appearance of the aorta so affected. Since then everyone has recognized it at a glance. It seems to be one of those simple triumphs of observation that makes one ashamed to have been so blind." The histological sections of the aorta in this case, originally (53 years ago) diagnosed as arteriosclerosis, have recently been reviewed by Dr. O. M. Wilbur, Jr., who found "absolutely typical syphilitic aortitis".

Currently under observation is a 57 year old man (M.B., J.H.H. 706852) with a very loud aortic diastolic murmur of strikingly musical quality. Serological tests for syphilis including treponemal immobilization tests are negative and the aorta is not dilated. The murmur, which is audible to both the patient and his wife, clearly had its onset in the Fall of 1954 since frequent physical examinations had been performed. The cause in this case is completely obscure and the problem is comparable to that in Case 2 above.

The phonocardiographic characteristics: The first oscillographic recording of a musical aortic diastolic murmur was probably that made by Sir Thomas Lewis (see Fig. 18 of ref. 8) in 1913 using the Einthoven string galvanometer. The characteristic of the murmur displayed in this manner was the presence of regular vibrations indicative of a tone of pure frequency. Only the fundamental at about 180 c.p.s. was displayed. The same is true for the great majority of the other published oscillograms of musical murmurs. Usually this result was due to use of recording systems with too low frequency-response characteristics. When proper microphones and recording oscillographs are used and particularly in the so-called logarithmic phonocardiograms (i.e., phonocardiograms produced with low-frequency intensity compression), one is able to demonstrate at least the second harmonic in addition to the fundamental. Such was the case in one recording of Wells, *et al.* (see Fig. 32 of ref. 9) using equipment of the Sanborn Company and in a recording made by Dr. Wm. R. Scarborough using

a Hathaway string galvanometer with a natural frequency of 1000 c.p.s. (see Fig. 20C of ref. 2).

As previously reported (1, 2) the basic spectral phonocardiographic characteristics (see Fig. 2) of musical diastolic murmurs are (1) the presence of several conspicuous harmonics and (2) the presence, as a rule, of a curvature in the harmonics which first ascend and then descend. A three-dimensional model of a murmur of this type displaying the harmonics and their curvature has been presented elsewhere (Fig. 21 of ref. 2). Geckeler, *et al.* (Fig. 7B of ref. 13) have presented the spectrogram of a musical aortic diastolic murmur from a patient with rheumatic heart disease. Precisely the same features were demonstrated.

The murmurs of eleven of these patients have been studied.* All but two of the patients are syphilitic. As might be anticipated, the murmur is different in each case. Since all but one of these patients are still living the anatomical basis for the variations, both from patient to patient and in some cases from cycle to cycle, is unknown. Among the eleven patients with musical diastolic murmurs variations have been observed in the following respects:

(1) In the time interval between the beginning of the murmur and the frequency peak (compare Figs. 2 and 9).

(2) In the frequency level of the fundamental and other harmonics (compare Figs. 6 and 9).

(3) In the frequency span between the nadir and the zenith of the harmonics (compare Figs. 2 and 9).

(4) In the presence or absence of a systolic murmur with similar harmonic constitution (see Fig. 4A).

(5) In the degree of cycle-to-cycle variation in the diastolic murmur (see Fig. 3).

(6) In the presence or absence of an abrupt change in the musicality of the diastolic murmur part way through (see Fig. 5).

(7) In the duration of the musical murmur, particularly with regard to its interruption by atrial contraction (see Fig. 9).

(8) In the presence of an increase in intensity without corresponding increase in frequency in mid-diastole, with atrial contraction or just before premature contractions (see Figs. 2, 6, and 7).

(9) In the alteration in tonality on transmission to the several precordial loci (see Figs. 6, 11, 12, and 13).

(10) In the presence of variations with respiration, specifically an intensification early in expiration (see Figs. 12 and 13).

The murmur of retroverted cusp is often among the loudest encountered in clinical practice. The murmur may be heard very widely over the body (27)

* Faint musicality, displayed as indistinct harmonic organization in the spectral phonocardiogram, is encountered rather commonly in the murmur of aortic regurgitation

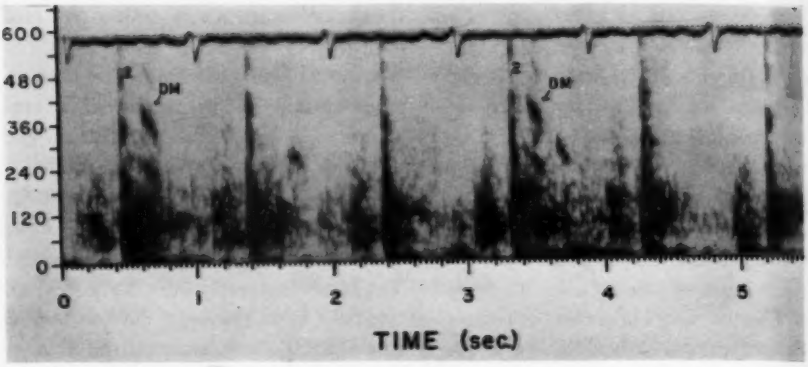

FIG. 3. Highly variable musicality of aortic diastolic murmur in patient with syphilitic aortitis. The structure responsible for the musicality is probably unstable. Note presence of both musical and non-musical elements of the diastolic murmur.

and even be audible at a distance (29). In recording these murmurs the normal heart sounds may be nearly lost in efforts to avoid "overloading" of the magnetic tape. In three cases (displayed in Figs. 6, 12 and 13), at least the fundamental was recorded over the olecranon and over the lower abdomen and back.

Beat-to-beat variation in all types of musical murmurs as well as variation in tonality of a murmur from time to time as with changes in cardiac compensation has been described by de Castro (22). This phenomenon is demonstrated in Fig. 3. Whether this variability is the result of respiratory phase (as in Fig. 12) cannot be stated from the data available in this patient.

In one patient the replacement of a strikingly musical aortic diastolic murmur by a "garden-variety" of murmur has been documented. The interval between the two observations was three years. The first recording was made in early 1952 on a phonograph disc. The analysis of this recording is shown in Fig. 2. When studies were repeated in February, 1955, it was discovered that the murmur of aortic regurgitation was of the conventional type. Usually the prognosis is much worse than would be suggested by the experience in this case. Another patient in this series (illustrated in Fig. 6) has maintained a musical murmur unchanged for over two years.

Occasionally a patient with a musical diastolic murmur of the type under discussion will also demonstrate a systolic murmur with the same harmonic pattern. It is possible that in such cases the diseased cusp prolapses into the aorta during systole as well as retroverting into the ventricle in diastole. Such a case, a patient with syphilis, is illustrated in Fig. 4.

In one patient a short but musical sound followed the second heart sound and was itself followed by a more conventional type of aortic diastolic murmur. This was interpreted as indicating that the diseased cusp retroverted rather explosively with accompanying musical vibration but was not set into con-

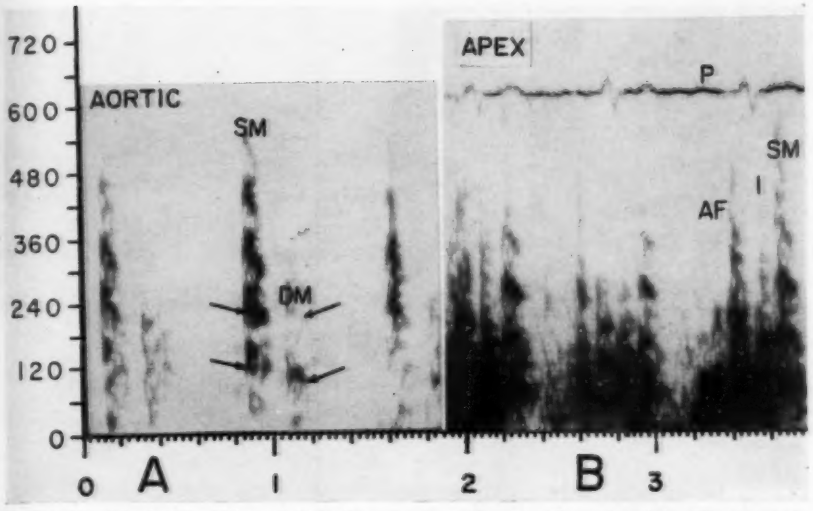

FIG. 4A. Musical systolic and diastolic murmurs of presumed aortic origin. The presence of identical harmonics (see arrows) suggests that the same vibrating structure is responsible for both. B. Noteworthy are 1—the distinct musicality of the systolic murmur at the apex, 2—the striking late diastolic murmur (? Austin Flint), and 3—the prominent atrial heart sound.

tinued vibration by the regurgitant stream. (See Fig. 5.) This case represents another example of the double nature of the murmur which may be present in these cases. The musical murmur is created by the vibrations of the elastic valve flap and the noisy murmur by turbulence in the regurgitant stream.

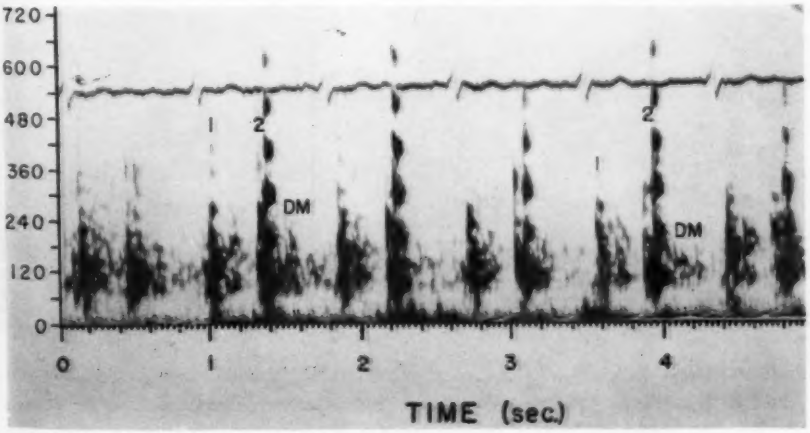

FIG. 5. A circumscribed early diastolic musical component of a longer diastolic murmur in syphilitic aortic insufficiency. Note presence of both musical and noisy components.

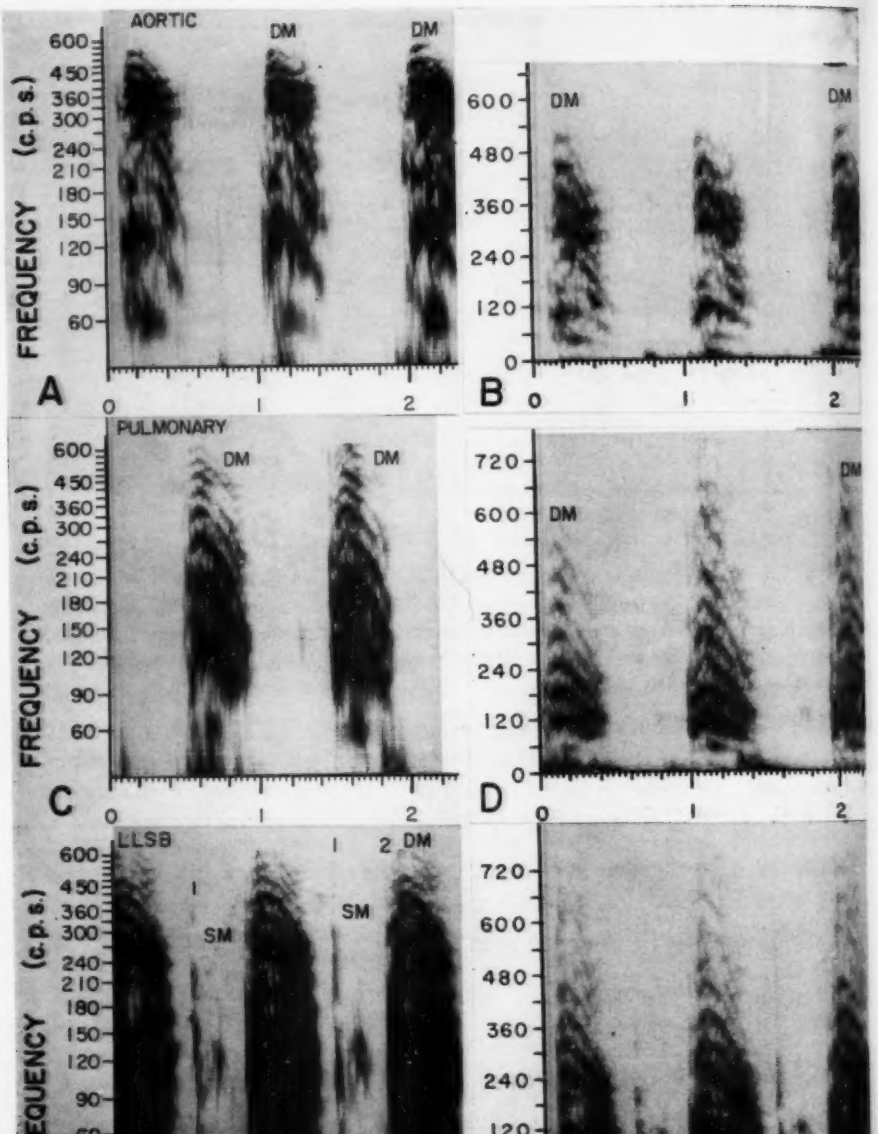

FIG. 6. Logarithmic and linear frequency displays of recordings from aortic (a, b), pulmonary (c, d) and left lower sternal (e, f) areas. Note the evidence of resonant absorption in a frequency band from 150 to 300 c.p.s. (aortic area). Also note the intensification of the murmur in the latter part of diastole.

FIG. 7. Oscillographic phonocardiogram in patient M. G. (case 2 above). In addition to the crescendo-decrescendo construction at the beginning, note the increase in intensity of the murmur in mid-diastole.

The frequency span between the two extremes (zenith and nadir) of each harmonic "chevron" is virtually identical on a percentage basis. This point is illustrated by comparison of linear and logarithmic recordings of the same sounds. Although on the linear scale the frequency span of the curvature in the harmonics is quite different from harmonic to harmonic, on the logarithmic scale it is identical. See Fig. 6; also 9B and 14A.

Shown in Fig. 7 is an oscillographic recording made by Dr. Wm. R. Scarborough in patient M. G. (Case 2 above). Only the fundamental is demonstrated as in most published oscillograms. Not only must the frequency response of the recording apparatus be appropriate (see discussion above) but the intensity of the second harmonic must be at least one-tenth as great as that of the fundamental if both are to be displayed in their true relative proportions. Here is illustrated the superiority of spectral phonocardiography in the display of the great dynamic range of cardiovascular sound. At the beginning of the diastolic murmur it is well demonstrated that there is an interval before intensity attains its peak according to the principle displayed in Fig. 8. After this peak there is a gradual decline in intensity. In the long diastolic periods after the extra-systoles a peculiar phenomenon is observed, namely a secondary increase in intensity. It would appear that as the retroverted cusp falls back to a more central position in respect to the regurgitant jet it vibrates with larger amplitude. This same phenomenon, increased intensity without corresponding increase in frequency, is demonstrated in the spectrogram in Figs. 2 and 6B. Also of much interest is the fact that atrial systole and the extrasystole are accompanied by a momentary increase in the intensity of the murmur! This is followed by a somewhat gradual decrescendo in frequency and intensity in the

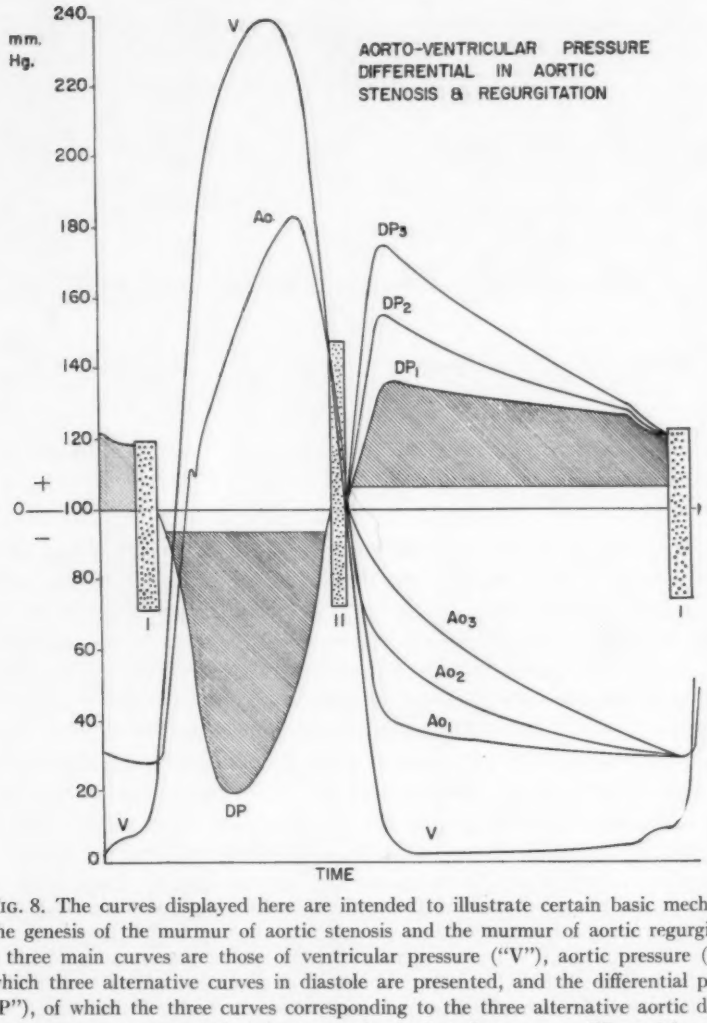

FIG. 8. The curves displayed here are intended to illustrate certain basic mechanisms in the genesis of the murmur of aortic stenosis and the murmur of aortic regurgitation. The three main curves are those of ventricular pressure ("V"), aortic pressure ("Ao"), of which three alternative curves in diastole are presented, and the differential pressure ("DP"), of which the three curves corresponding to the three alternative aortic diastolic pressure curves are presented. A basic premise is that the pressure differential across an orifice is intimately related to the intensity-frequency characteristics of the murmur produced. From what is known about the shape of the ventricular and aortic pulse pressure curves in aortic stenosis it is evident that the curve of pressure differential will in systole have the shape shown in the diagram. The murmur of aortic stenosis has a similar curve as to intensity and peak frequency (the so-called "diamond" systolic murmur of conventional oscillographic phonocardiography and the "Christmas tree" murmur of spectral phonocardiography). The configuration of the diastolic portion of the differential pressure curve helps elucidate several features of aortic diastolic murmurs as they are encountered in practice. Since there is likely to be a certain threshold of differential pressure which must be exceeded before murmur is created, the occasional, in fact rare, demonstration of a gap

case of atrial systole, a more abrupt decline with the premature ventricular systole. The increase in intensity is probably on the same basis as that which occurred in mid-diastole with long diastolic periods: the vibrating retroverted cusp is moved nearer the center of the regurgitant stream and vibrates through a greater excursion thereafter.

In Fig. 7 note, furthermore, that the intensity peak of the early diastolic crescendo is greater in the normal cycle following the compensatory pause than it is in the extrasystolic cycle. This is clearly related to differences in aortic pressure which in turn are related to differences in stroke volume.

Hemodynamic factors in the genesis of these murmurs: Two components are believed to be present in the type of murmur under discussion: 1) a musical component related to the regular vibrations of the elastic retroverted lip of aortic cusp or similar valve remnant, and 2) a noisy component resulting from turbulence of the regurgitant stream of blood. In many of these cases the musical component is so exceedingly loud that because of the adjustment of amplification to avoid "overloading" in recording and indeed as a result of physiological masking during auscultation, the noisy component is inapparent, both in the record and to the ear. However, both are evident in cases of less intense musical component (see Figs. 3 and 5).

(In the murmur of calcific aortic stenosis (see below) it is also possible to identify both musical and noisy components. In that instance evidence relating the musical element to the virbrations of the stenotic valve structure and the noisy element to turbulence produced by the jet can be assembled. It seems likely that in the sounds of normal valve closure there are contributions both from the valve structure itself, set into vibration by the impact of the coapting cusp margins, and from turbulence in the nearby blood created by the valve movement.)

The curvature in the harmonics of these diastolic murmurs is related to changes in the velocity of regurgitation which in turn is related (although not in a 1:1 manner) to variations in the pressure differential between the aorta and the left ventricle. There is first acceleration, then deceleration ("negative acceleration") of the regurgitant stream. Murmurs arising at the aortic orifice may be intimately related to the pressure differential across the orifice and its variations in the cardiac cycle. Charting of this differential helps clarify thinking about the physical basis of variations in murmurs. Figure 8 presents the

between S2 and the beginning of the diastolic murmur (26) is afforded explanation. Similarly at the end of diastole the diastolic murmur sometimes stops abruptly with the P wave of the electrocardiogram or with the atrial heart sound. This phenomenon is probably due to fall of differential pressure below the murmur threshold as a result of the increment of intraventricular pressure produced by atrial contraction. Within limits, the larger the anatomical leak at the aortic valve, the lower the differential pressure and the smaller the diastolic murmur, on first thought a paradoxical phenomenon. The parallel variation of intensity and peak frequency (or frequency span) in a given murmur has been demonstrated for non-musical murmurs and in general the same relationship obtains in musical murmurs.

course of the pressure differential curve as derived from curves known for aortic stenosis and regurgitation (43). Since the frequency changes are more directly dependent on changes in velocity, since velocity and pressure differential almost certainly do not bear a one-to-one relationship to each other, and since there is likely to be a time lag of the velocity curve as compared to the pressure differential curve, exact duplication of the pressure differential curve by the frequency pattern of the murmur is not to be expected.

It appears that there is a threshold pressure difference below which the murmur and possibly regurgitation does not occur. For instance, with atrial contraction and the elevation of ventricular pressure produced thereby, the

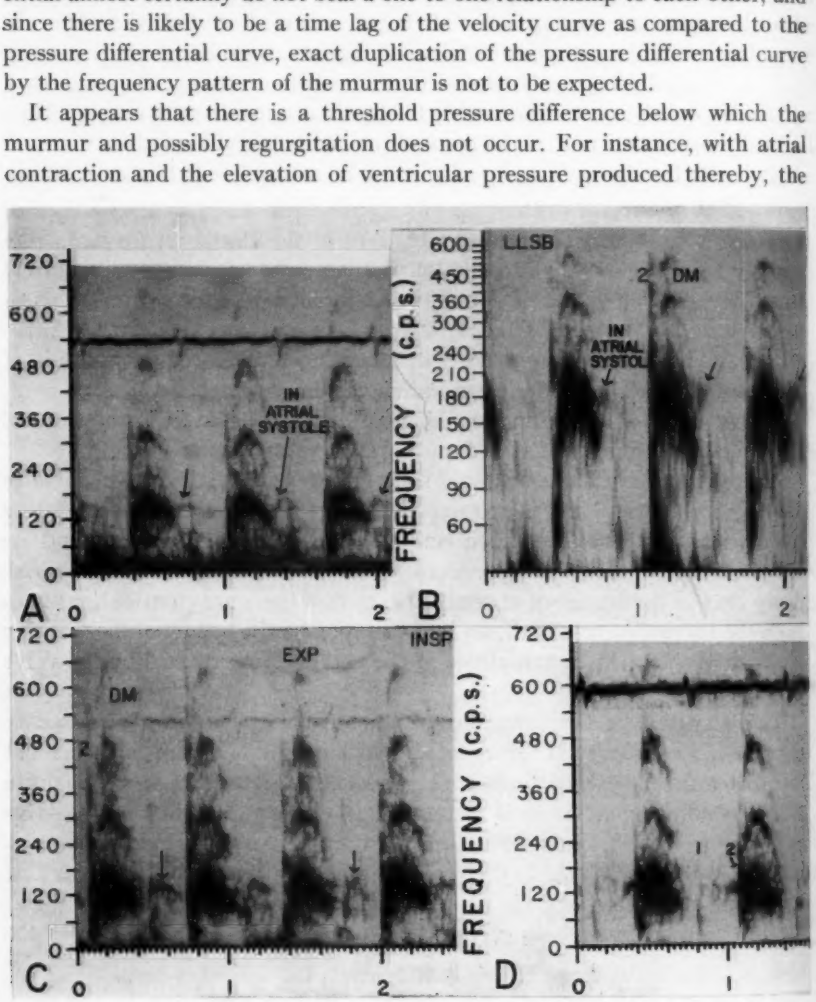

FIG. 9a, b, c, and d. These are all recordings made at different times from the lower left sternal border in a patient with aortic regurgitation on the basis of syphilis. The typical chevron harmonic pattern is demonstrated. Particular attention is drawn to the evidence of continued vibration of the anomalous structure, with production of a faint harmonic, during atrial systole (a and b), during early ventricular systole (c), and during late ventricular systole (d).

diastolic murmur comes to an abrupt halt (see Fig. 9C, also Figs. 6E and F). In some cases atrial contraction causes an abrupt change in the slope of the intensity and frequency curves but not an abrupt halt in the murmur. This more gradual cessation is demonstrated in Fig. 7.

At times a circumscribed sound which is clearly not atrial sound or third heart sound occurs at the termination of a diastolic murmur of aortic or pulmary regurgitation. It is possible that this represents a closure sound, that is, that when the aorto-ventricular pressure differential falls below a certain critical value the leaking orifice, previously held open, closes with production of a sound. A possible re-closure sound terminating a diastolic murmur has been demonstrated in the case of a Graham Steell murmur (23).

In order to study changes in the murmur with alteration in the aorto-ventricular pressure differential, systemic arterial pressure was raised by the infusion of norepinephrine intravenously and was depressed by the stat intra-

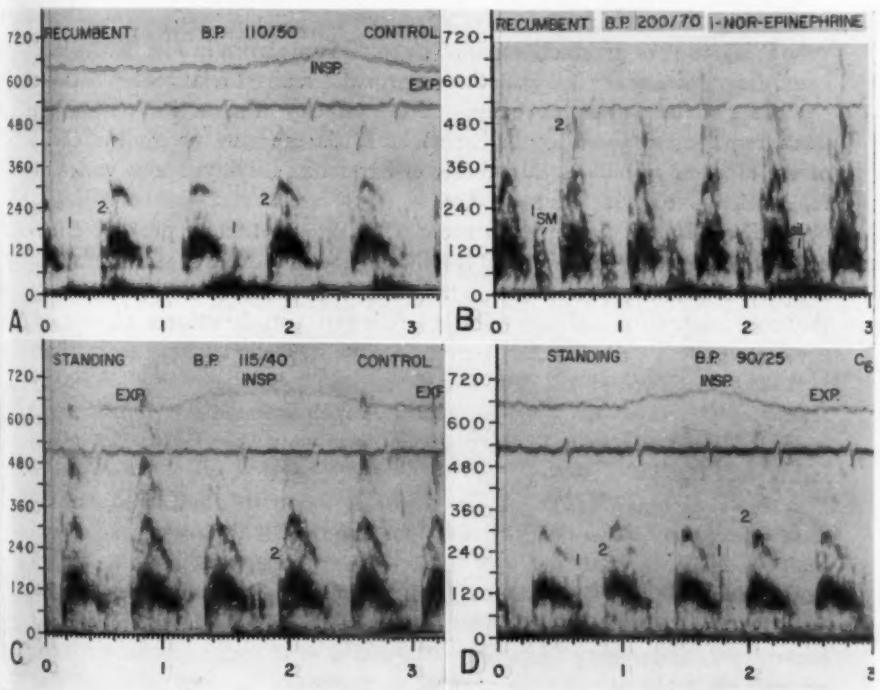

FIG. 10a, b, c, d, and e. Here are displayed (in the same patient whose sounds are displayed in Figs. 9 and 11) the findings at LLSB in the recumbent position before (Fig. 10a) and after (Fig. 10b) the administration of l-nor-epinephrine intravenously and in the standing position before (Fig. 10c) and after (Fig. 10d) the administration of hexamethonium intravenously. Fig. 10e presents a synthesis of the findings. See text for detailed discussion.

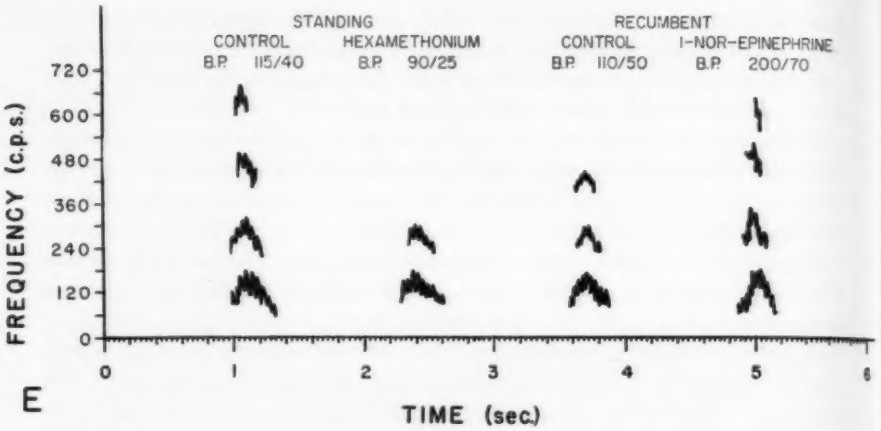

FIG. 10e

venous injection of hexamethonium. The results are shown in Fig. 10. As indicated diagrammatically in Fig. 8, there is probably a direct relationship between the effect of these pressure changes on the velocity of regurgitation and the peak frequency attained by the harmonics of the murmur. Over-all intensity of the murmur and the total number of harmonics displayed also varies directly with systemic arterial pressure.

Further evidence of the pertinence of the aorto-ventricular pressure differential is provided by the effects of respiration and of the longer ventricular filling periods following premature contractions. Venous return to the left side of the heart is increased early in expiration. As a result stroke volume is increased, aortic pressure may be increased and if so, the diastolic murmur may be accentuated (see Figs. 12 and 13). The stroke volume in the cycle immediately following the compensatory pause associated with a premature contraction is increased and an increase in the diastolic murmur in that cycle may be observed (see Fig. 7).

Demonstrated in Fig. 9D is slight representation of the fundamental of the diastolic murmur occurring late in ventricular systole. This appears to indicate that the vibrating structure may be set into movement before the end of ventricular systole, at least before the end of ventricular systole as defined by events on the right side of the heart. This finding suggests, furthermore, that aortic regurgitation may begin before the end of ventricular systole. Such has been previously suspected because of the change in the shape of the ventricular ejection curve and the striking "systolic collapse" of the aortic pressure curve in aortic regurgitation (43, 37).

That the retroverted cusp is itself very intimately concerned in the genesis of this murmur is indicated by the following points: 1) In other cases of aortic

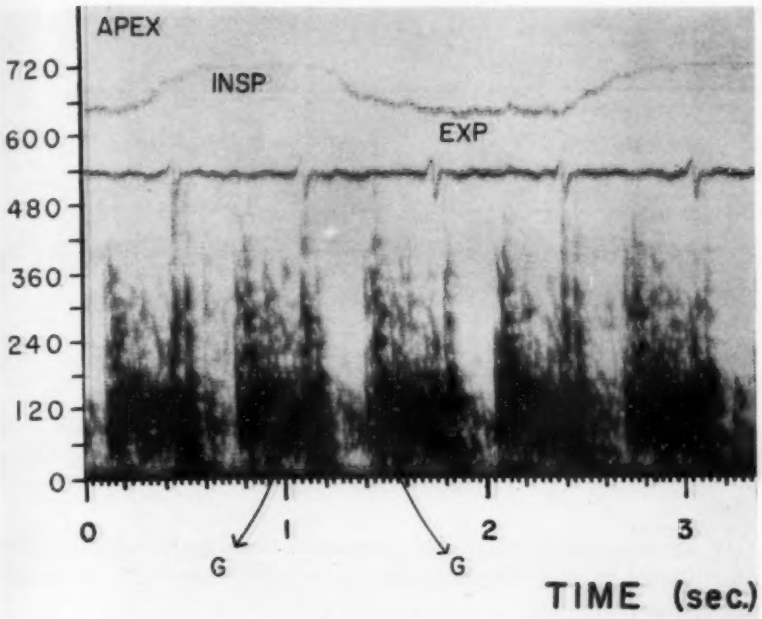

FIG. 11. As was previously described (2) in another patient with musical diastolic murmur the component of the diastolic murmur which is best transmitted to the apex is that in the frequency range of the natural frequency of the thorax, i.e., the fundamental. The recording here from the apex is in the same patient as represented in Figs. 9 and 10. A protodiastolic ("G") and possibly a presystolic gallop are present.

regurgitation with non-musical murmur the same anatomical situation exclusive of the retroverted cusp is present. This type of murmur is rare but perfectly characteristic. Its association with retroverted cusp is strong enough to make it unescapable that that structure is intimately concerned in the genesis of the murmur. 2) The phenomenon illustrated in Fig. 7 is difficult to explain unless one assumes the presence of a vibrant retroverted flap of valve cusp which, because it is hinged, is free to change its orientation to the regurgitant stream. 3) The fact that these are, as a group, among the loudest murmurs known to medicine may be an argument for the important participation of a flap structure in their genesis rather than mere blood turbulence, as in the case of other murmurs of aortic regurgitation.

It is likely that a Bernoulli phenomenon plays a prominent part in the production of this musical murmur as well as of some others. It is not necessary that the retroverted cusp have intrinsic elasticity. It might be perfectly limp, like a flag in the wind. The restoring force tending to return it toward the center of the regurgitant stream may be Bernoulli in nature. It is battered to and fro

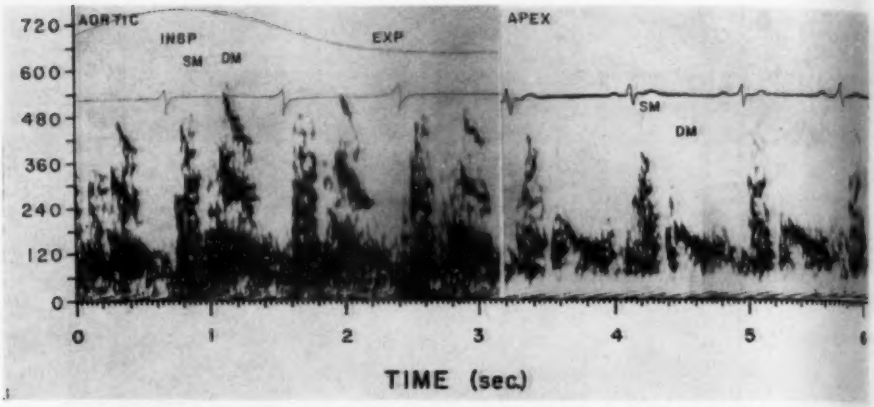

FIG. 12. Recording at the aortic and apical areas of a musical aortic diastolic murmur which was audible as far as each olecranon and the lower abdomen and back. Note variation of diastolic murmur with respiration and the change in tonality on transmission to the apex.

by the opposing direct force of the regurgitant stream and the Bernoulli force. In the process the flap modulates the regurgitant stream with conversion of much energy into sound.

Factors of selective transmission and resonant absorption: Both to the ear and in the spectral phonocardiogram pronounced change in the quality of the diastolic murmur occurs on transmission to the apical area or left axilla. The murmur becomes much lower pitched. The spectrogram reveals that the fundamental which is usually at the level of 120–180 c.p.s. is transmitted to the remote area a great deal better than the overtones (Figs. 11 and 12; also see Fig. 20B of ref. 2). The natural vibrational frequency of the adult thorax is approximately the same as the fundamental of these murmurs (24). Herein probably lies the basis for the selective transmission observed. The finding permits a conclusion much broader than its application to these relatively uncommon murmurs: in association with a loud murmur of aortic regurgitation an apical diastolic murmur of low pitch and rumbling quality may still be of aortic, not mitral, origin. The change in pitch of musical aortic diastolic murmurs on transmission to the apex was described by de Castro (22).

In two cases there was a difference in the quality of the diastolic murmur as recorded at the aortic area and as recorded at the left lower sternal border. At the aortic area there was pronounced attenuation of the frequencies between bout 150 and 300 c.p.s. This phenomenon is illustrated in Figs. 6 and 13. (See also Fig. 20A of ref. 2.) Although the anatomical basis of this phenomenon is not clear, it has the characteristics of resonant absorption. The presence of an aneurysm of the ascending aorta filled with thrombus might have this effect.

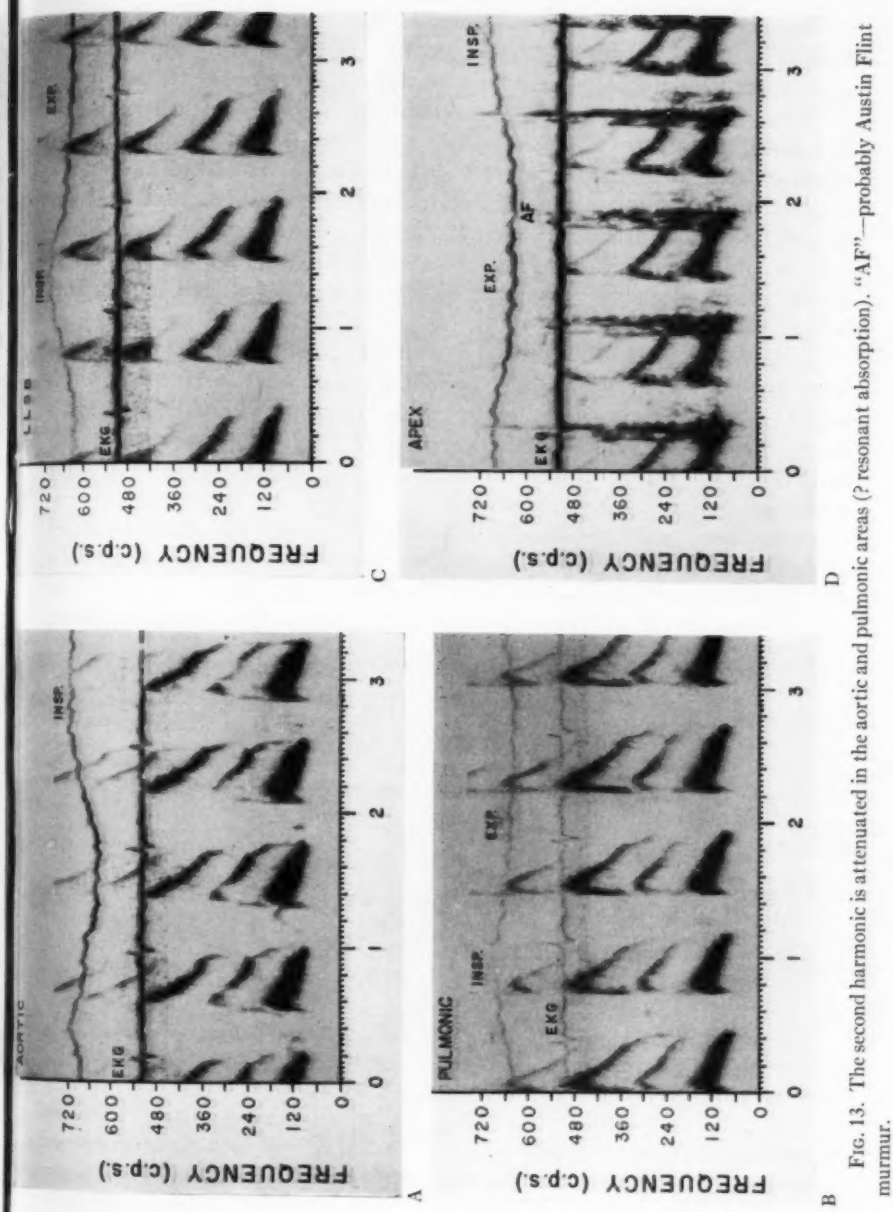

FIG. 13. The second harmonic is attenuated in the aortic and pulmonic areas (? resonant absorption). "AF"—probably Austin Flint murmur.

In neither patient, however, was there evident aortic dilatation by X-ray. Whether medial and intimal changes produced in the aorta by syphilis could account for the phenomenon cannot be stated.

Bizarre late diastolic murmur with dissection of the ascending aorta: In Fig. 14A and B is presented a correlation of the clinical and anatomical findings in a patient with Marfan's syndrome (6). In life there was a loud basilar diastolic murmur of typical decrescendo character after the second heart sound. With the longer diastolic periods of slower heart rates and particularly those following premature ventricular contractions there was in addition a loud musical sound in late diastole which sounded like a note played on a "bull fiddle". This is illustrated in Fig. 14A.

Autopsy revealed a healed dissection of the ascending aorta with double-barrel configuration (Fig. 14B). There were three anomalous structures which might have vibrated musically: 1) the tube of true aorta within the false aortic channel, 2) the string-like fibrous strands traversing the false aortic channel, and 3) the lip of the sinus of Valsalva which had been dissected free of its outer coats and of its attachment to the rest of the aorta at the site of the diverticulum. Hemodynamically it is difficult to visualize the situation which would set any one of these three structures into such violent vibration near the end of a long diastolic period and only at that time. It is possible that the margin of the pocket marked "diverticulum" was responsible. Early in diastole one might

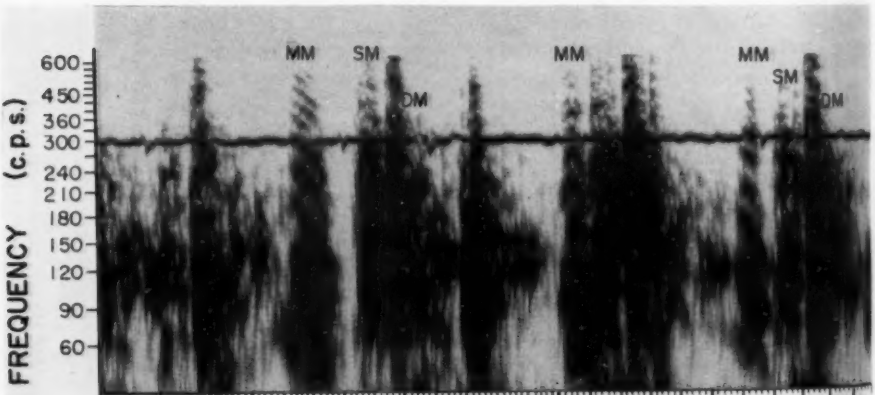

FIG. 14A. Heart sounds in a patient with Marfan's disease and dissecting aneurysm of the aorta. Bigeminy is present. Note strikingly musical late diastolic murmur. Logarithmic frequency scale. A transient musical element early in diastole is present in some cycles. B. Dissecting aneurysm of the aorta in patient with Marfan's disease and musical aortic diastolic murmur.

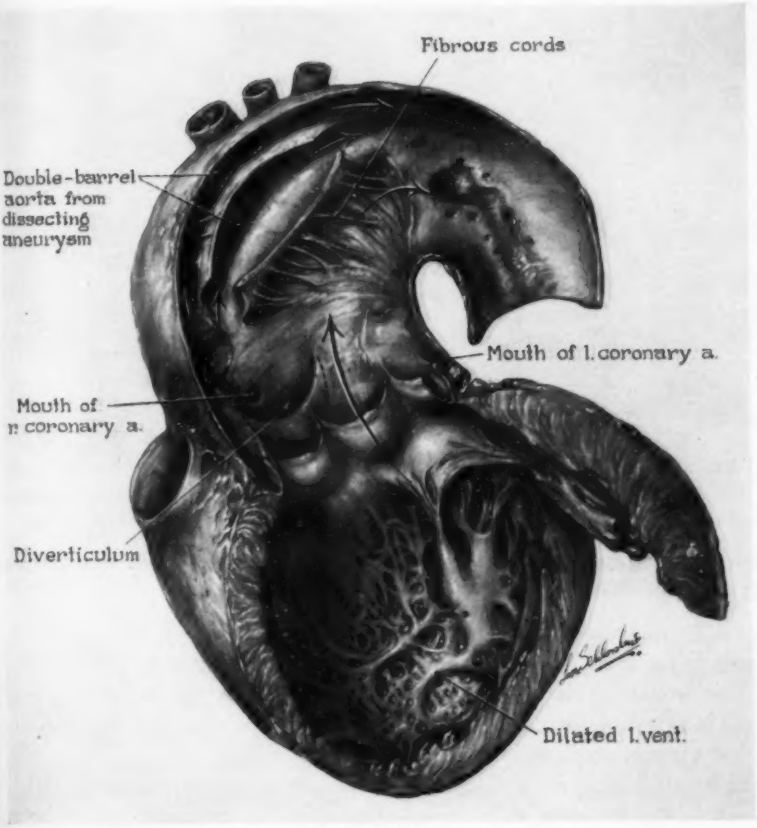

FIG. 14B

expect this structure to be pushed (or pulled) out of the way of the regurgitant stream by the expansion of the aortic wall with the preceding ventricular discharge. With fall in aortic pressure this margin might return to a more central position and be set into vibration by the regurgitant stream.

MUSICAL EXTRACARDIAC DIASTOLIC MURMURS

In four patients with chronic rheumatic heart disease and mammoth cardiomegaly and in one patient with seemingly normal cardiovascular system but severe rheumatic fever in the past, a musical early diastolic murmur has been recorded. Because of the correlation of the murmur with other cardiac findings and because of the absence of signs pointing to pulmonary or aortic regurgitation the murmur is believed to be extracardiac in origin. The rubbing of roughened pericardial surfaces is perhaps the most likely mechanism of these murmurs. The absence of variation with respiration makes it less likely that move-

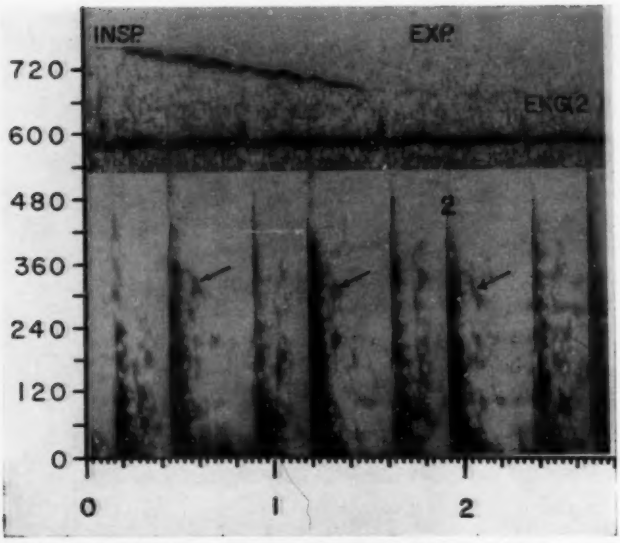

FIG. 15. Faint early diastolic squeak in patient with history of severe acute rheumatic fever but ostensibly normal cardiovascular system otherwise.

ment of air in a lappet of lung is responsible. A musical early diastolic murmur present in the early post-valvulotomy period in a patient with mitral stenosis has been presented elsewhere (Fig. 14B of ref. 2). Since the sound later disappeared in this case, further support is provided for the view that this particular musical early diastolic murmur is of pericardial origin.

The importance of recognizing the true nature of the sound is exemplified by the case in Fig. 15. Here, as in the other cases, the murmur could easily be misinterpreted as indicating regurgitation at the aortic or pulmonary valve. In the patient recorded in Fig. 15 there was no other suspicion of cardiovascular residuum of the previous rheumatic fever.

A seemingly similar murmur has been attributed by Gallavardin, *et al.*, (38) to minimal aortic regurgitation ("bruit musical diastolique intermittent, signe d'insuffisance aortique minima, sans souffle"). Although this mechanism is possible in the patient illustrated in Fig. 15, the striking similarity to the early diastolic squeaks in cases in which pericardial origin is likely leads us to believe that this is the mechanism here also. The murmur of minimal aortic regurgitation is often high pitched but never, in our experience to date, truly musical.

The patient whose recordings are shown in Fig. 16 has extreme cardiomegaly with trivalvular stenosis and regurgitation on the basis of rheumatism. The early diastolic squeak was present mainly at the lower end of the sternum which heaved impressively with each right ventricular systole.

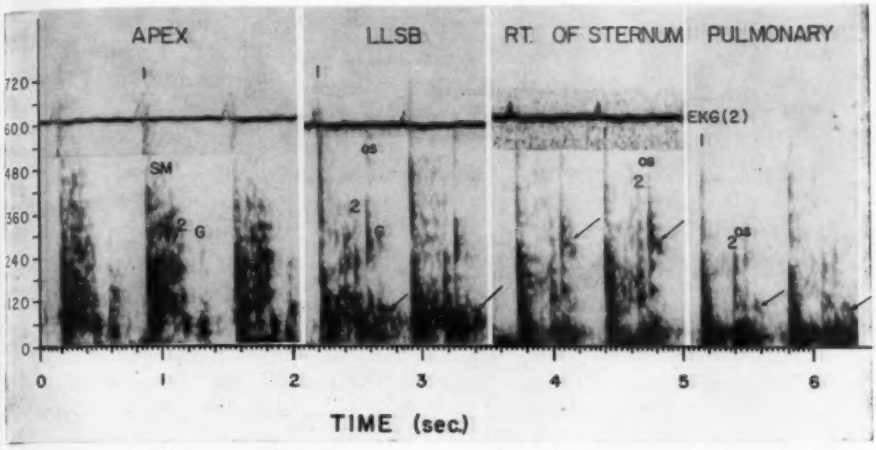

FIG. 16. Musical early diastolic murmur in region of lower sternum in patient with rheumatic trivalvular disease and mammoth cardiomegaly. It is of interest that both an opening AV (probably mitral) snap and protodiastolic gallop are demonstrated. The squeak begins with the former.

Huchard (28) described a 30 year old hypertensive patient with a very loud musical diastolic murmur which was, by exclusion of valvular disease at necropsy, considered to have been of cardiopulmonary origin but which immediately suggested to Duroziez and other clinicians, "rupture valvulaire des sigmoides". The absence of peripheral signs of aortic regurgitation was consonant with the findings of necropsy Calo (see Fig. 48 bis of ref. 11) presented the phonocardiogram of a 52 year old man, "an old bronchitic", who had a musical diastolic murmur heard all over the chest and even by the patient himself. No modification occurred with respiration or change in position. More details of the same patient are provided in ref. 39.

Hirschfelder (40) quotes Laennec's description of musical cardiopulmonary murmurs. Although Laennec conceived of this type of murmur being located in diastole, it is possible that it might occur in either diastole or systole. "In certain persons the . . . anterior borders of the lung extend in front of the heart . . . If one examines such a person when his heart is beating more forcibly than usual, the diastole of the heart, compressing these portions of the lungs and forcing the air out of them, alters the breath sounds in such a way that it imitates a blowing murmur or the sound of a wood file . . . it disappears almost entirely when the patient is made to hold his breath for a few moments".

MUSICAL SYSTOLIC MURMURS

Extracardiac musical systolic murmurs. Elsewhere (Fig. 14A of ref. 2) the spectral phonocardiogram of a musical late systolic cardiorespiratory murmur has been presented. Since the patient had pronounced cardiomegaly and since

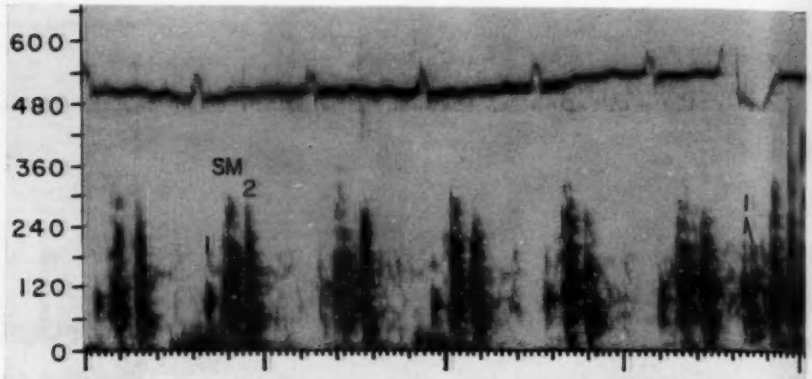

FIG. 17. Croaking systolic murmur as residuum of pericardial friction rub.

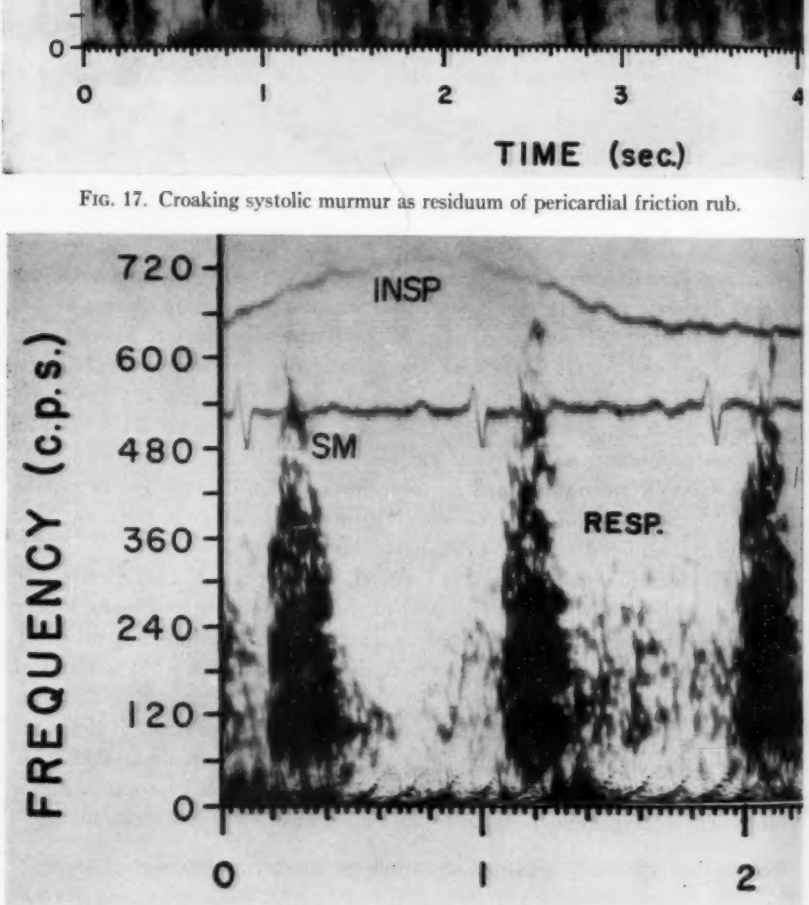

FIG. 18. Systolic murmur of aortic stenosis (pulmonary area). Both musical and noisy components are present. Photographic recording.

the squeak was present in the left mid-precordium only during inspiration, the movement of air through tiny bronchioles in a lappet of lung was probably responsible for the squeaking sound. Hirschfelder (40) suggested that some of these musical murmurs might in fact be piping rales. An alternative possibility is the rubbing of serosal surfaces, normal (12) or abnormal.

Circumscribed mid-systolic murmurs, often introduced by a systolic click, have been considered to be the result of pericardial roughening and/or adhesion (3). The case presented in Fig. 17 is instructive from two points of view: 1) The evolution of the murmur from acute pericardial friction rub to circumscriped mid-systolic murmur and finally its disappearance were followed stepwise. 2) The systolic sound had a creaking or croaking quality to the ear and displayed considerable musicality in the spectral phonocardiogram.

Geckeler *et al.* (13) have presented spectrograms of a musical systolic murmur (referred to by them as a "grunt"; "bull-frog" murmur is another appropriate designation) which was heard in the second right intercostal space for about ten days after mitral commissurotomy. The authors did not think it was pericardial in origin. However, reference to the case presented in Fig. 17 makes the pericardium still a possible source of the sound.

Calcific aortic stenosis. The raspy systolic murmur of calcific aortic stenosis owes its timbre to the presence of harmonics (Fig. 18; also see Fig. 2 of ref. 3).

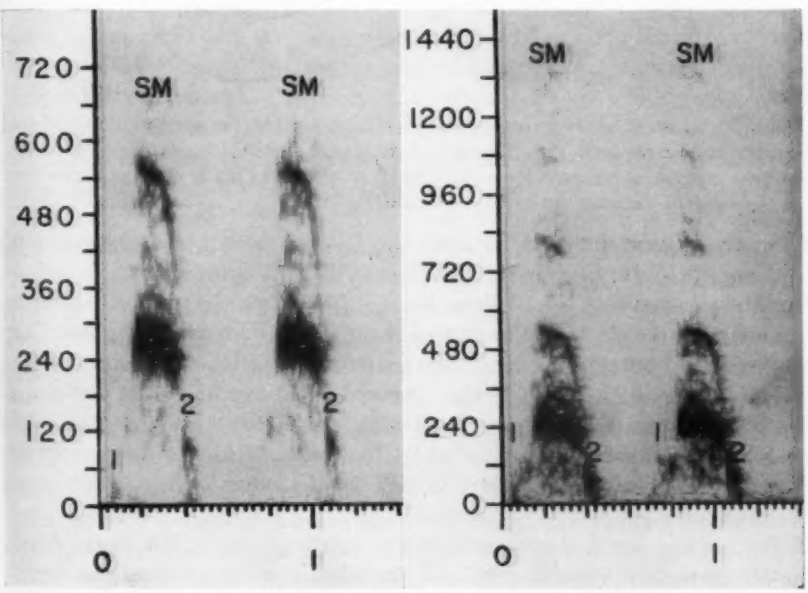

FIG. 19. In this patient with calcific aortic stenosis the systolic murmur was strikingly musical in quality at the apex and left mid-precordium and much more so there than it was n the aortic area or base of the neck.

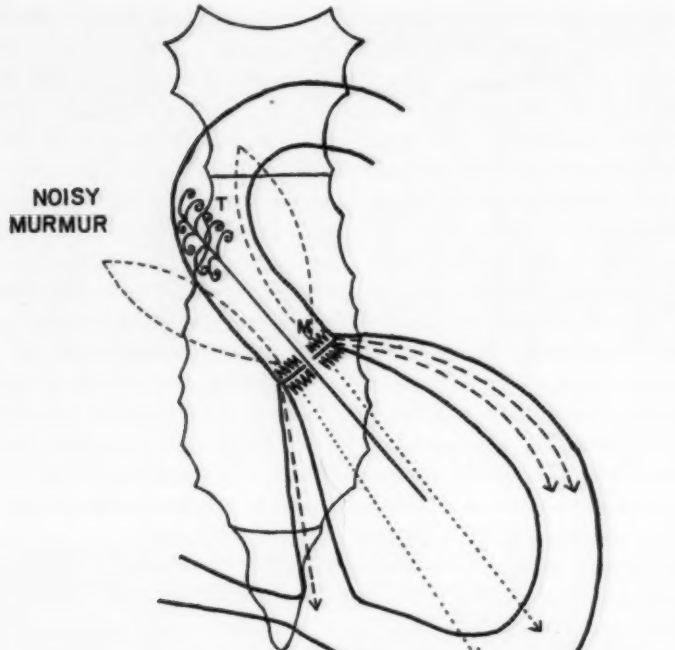

FIG. 20. In aortic stenosis the murmur may be musical at the apex and left mid-precordium, noisy in the aortic area. The musical component may arise in the stenotic valve and the noisy component higher in the aorta. The jet noise may be highly directional and there may be zones of maximum intensity as indicated by "rabbit ears" in dashed lines.

Often the musical timbre is much more striking in the left mid-precordium or at the apex (36, 14) (see Fig. 19) than it is at the base of the heart. The basis of this phenomenon may be as follows (see Fig. 20): Often the point of maximum musicality of the murmur is in an area of the precordium which represents the approximate frontal projection of the anatomical position of the aortic valve: 3rd interspace at left sternal border. It may be that over the lower portions of the heart a musical sound generated more specifically at the aortic ring is heard whereas at the aortic area and at the base of the neck—loci "downstream" from the aortic valve—secondary turbulence of random character dominates the murmur.

The musical murmur generated at the diaphragmatic fusion of the aortic cusp is the result of vibrations set up in that diaphragm by two opposing forces: the high pressure in the left ventricle tending to force open the fused cusps and the elastic forces of the valve diaphragm (aided by the Bernoulli forces)

tending to restore the aperture to its resting dimension. Because of its tenseness, particularly during systole, and close approximation to the chest wall, the greatly hypertrophied left ventricle probably favors transmission to the apex of the regular (i.e., musical) vibrations of the aortic diaphragm. On the other hand, the more random turbulence beyond the aortic valve dominates the sound heard at the right of the sternum and in the neck. In many cases (e.g., Fig. 18) musical and noisy components occur in combination in recordings from a given area.

The resonating properties of the ventricle may serve to intensify and purify the musicality of the murmur as heard at the apex. Because of the hypertrophy of the ventricle and the very high intraventricular pressure developed during systole the resonating frequency of the chamber is probably considerably higher than is normally the case. It might, for example, be in the range of 240–300 c.p.s., the range occupied by the fundamental in Fig. 19.

Intensive study of jet noise has been stimulated recently by the acoustical problems associated with the aeronautical use of turbojet engines. These studies (44) have demonstrated a striking directional characteristic of jet noise. The dashed "rabbit ears" in Fig. 20 are included as a hypothetical, as yet unmeasured, pattern of maximum intensity of the jet noise in aortic stenosis, based on the aerodynamic studies. The dashed lines of the "rabbit ears" are lines of equal intensity. The angle of this maximum noise pattern with the axis of the jet varies with several parameters of fluid flow and the fluid involved. The more dense the fluid (46), the less is the angle. In blood the angle might be negligible. The higher the frequency band of the jet noise, the greater is the angle (44). At any rate, the facts that immediately behind a jet source there is no sound or little sound and that the jet noise has strong directional properties are highly pertinent to this discussion.

The systolic murmur in some cases of aortic stenosis is strikingly musical with a virtually complete organization into a harmonic pattern whereas in other cases the murmur is merely a noise. Furthermore, clinical experience seems to indicate that higher grades of musicality are associated with more advanced calcification of the aortic valve. Within limits, the stiffer the diaphragm created by the fusion of the aortic cusps, the more musical would be expected to be the murmur produced. The stiffer diaphragm has more restoring force acting against the force of the ventricle which is tending to enlarge the stenotic orifice. There is probably very good basis for the clinical observations relating musicality to calcification.

The ejection stenosis murmur of congenital pulmonary stenosis is characteristically not musical. This fact may be related to the usual lack of fibrosis and calcification in the congenital diaphragm.

In earlier studies in models (see Fig. 2 of ref. 37) a partially musical murmur was created by flow through the perfectly rigid, "stenotic" orifice—the tip of

a syringe. In that case, however, it is likely that resonance in the tube beyond the syringe tip was responsible for the harmonic pattern.

In 1897 Dickinson (15) wrote "on the occurrence of musical mitral murmurs in connection with aortic stenosis". One of his cases may have been an instance of extracardiac musical murmur on the basis of massive cardiomegaly and/or pericardial affection. Another of his cases may have represented unusual transmission of the aortic murmur to the apex. However, he suggested another mechanism for a musical mitral murmur with aortic stenosis and the anatomical findings in his first case make his suggestion plausible. In this case the aortic stenosis was so severe that peripheral pulses were not palpable and at autopsy water would flow through the orifice only in drops or small trickles. The mitral valve was normal. Dickinson suggested that the marked elevation of left ventricular pressure which was undoubtedly present during systole forced the normal mitral valve with production of a very small leak and a very high-pitched murmur compared by him to the squeak of a mouse or guinea pig. He was aware, however, of musical murmurs produced by other mechanisms: "There may be musical murmurs of many kinds, as there are many sorts of musical instruments". We have not had occasion to observe a musical apical systolic murmur in a case of aortic stenosis in which the Dickinson mechanism seemed likely.

Musical systolic murmurs with mitral regurgitation. Several patients with acute rheumatic fever have been found to have musical systolic murmurs at the apex. These have all been crescendo holosystolic murmurs (see Fig. 21). In all these cases the harmonics have been fairly closely spaced with several in the frequency span below 750 c.p.s.

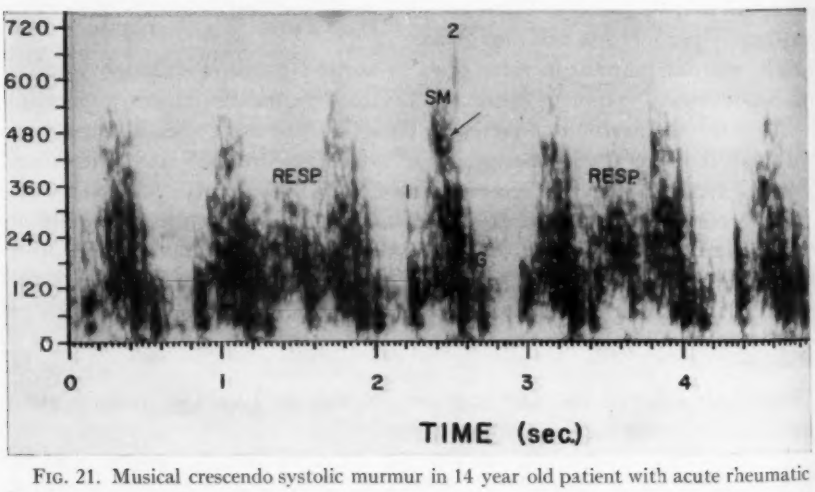

FIG. 21. Musical crescendo systolic murmur in 14 year old patient with acute rheumatic fever.

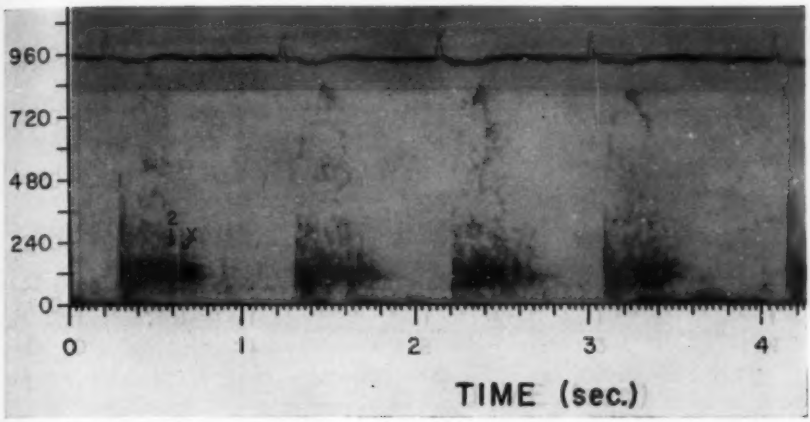

FIG. 22. Musical systolic murmur at apex in 50 year old patient with superannuated rheumatic heart disease and mitral regurgitation.

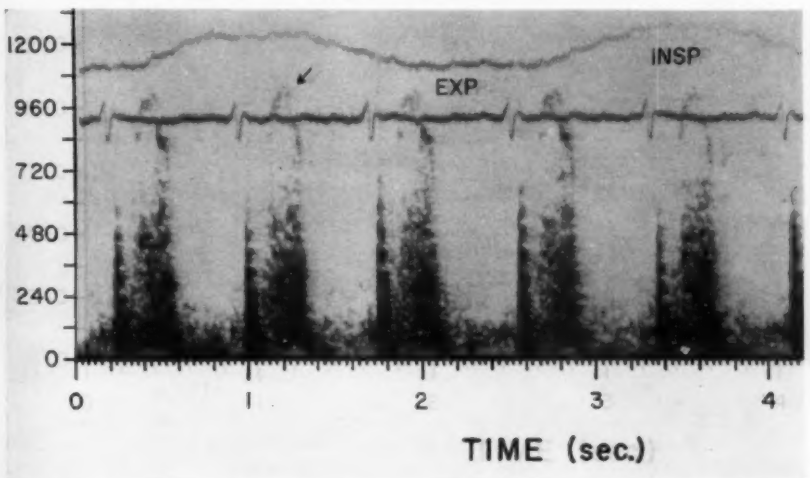

FIG. 23. Apex in patient with Marfan's disease. The physical basis of musicality of this crescendo systolic murmur is not apparent in the display on the 720 cycle scale. However on the 1440 cycle scale a distinct harmonic is visible.

In patients with mitral regurgitation on the basis of chronic rheumatic heart disease and in one patient with Marfan's disease and mitral regurgitation (partially on the basis of ventricular dilatation, possibly in part on the basis of redundant, hereditarily weak chordae tendineae) a delicately musical, high pitched systolic murmur, like wind blowing through the naked limbs of a tree, has been recorded and analyzed (see Figs. 22 and 23). These patients all have a conventional type of holosystolic murmur (plateau in Fig. 22; crescendo in

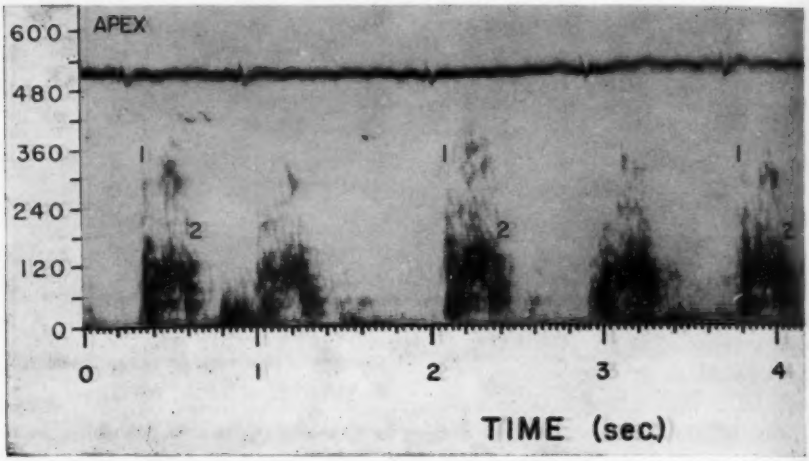

FIG. 24. Musical systolic murmur at apex in case of idiopathic myocarditis.

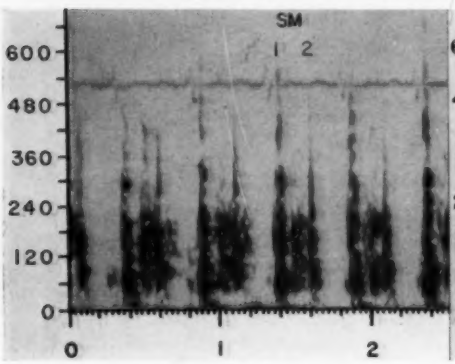

FIG. 25

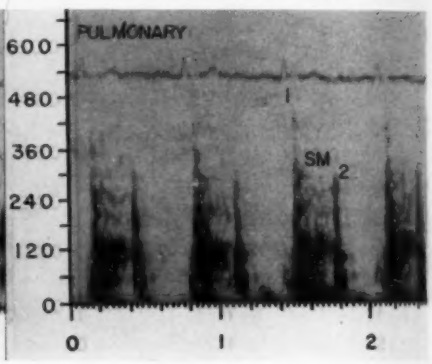

FIG. 26

FIG. 25. Musical systolic murmur in mitral regurgitation of rheumatic etiology.

FIG. 26. Pulmonary area in 18 year old patient with rheumatic heart disease. Note conspicuous fundamental and faint, inconsistent second harmonic.

Fig. 23) which is centered at 200–300 c.p.s. and which is of moderate intensity. The musical quality is the result of a tone located at 700–1000 cycles. In absolute terms this tone is much fainter than the systolic murmur at the lower frequency level but because of the response characteristics of the ear it makes much more of an impression on the stethoscopist and, in fact, dominates the timbre of the murmur. That it is an isolated sound separate from the non-musical murmur at the lower and more conventional frequency level is indicated by the fact that its frequency is not a multiple of that of the other. It is therefore itself a fundamental. (See Fig. 6 of ref. 13 for another example of the spectrogram of this type of murmur.)

In other cases of mitral regurgitation with musical systolic murmur the body of the murmur, with a frequency located in the vicinity of 120–240 c.p.s. is the fundamental. Figs. 24 and 25 are recordings from such cases. In such instances aortic stenosis with musical murmur transmitted to the apex must be excluded.

Whether ruptured mitral chordae tendineae can produce a musical systolic murmur is uncertain. We have verbal descriptions of patients in whom the presumedly abrupt onset of a loud musical systolic murmur was so explained. In the classical discussion of this subect (48) no clear description of a musical systolic murmur is provided. The systolic murmur, almost always loud, is variously described as harsh, coarse, and blowing as far as quality is concerned.

Hirschfelder (p. 110 of ref. 40) expressed the opinion that a musical systolic murmur often accompanies functional tricuspid regurgitation.

Ball-valve thrombus or myxoma of the atrium: In one case in which the right atrium was occupied by a ball-valve thrombus (L. C., J.H.H. 646029) and in a second with the left atrium as the site (H. K., J.H.H. 594258), a loud, musical systolic murmur was heard. Unfortunately recordings are available in neither patient. From the findings of post-mortem examination in the second and of operation in the first it seems likely that tricuspid or mitral regurgitation created by the action of the ball in holding apart the margins of the valve cusps was the basis of the murmur.

In the case of involvement of the right atrium there was at the left lower sternal border and at the very end of inspiration for the first three or four beats after the breath was held, a high pitched systolic "coo".

With the left atrial tumor the murmur was likewise highly changeable. During deep expiration there was a very harsh, screeching or grunting systolic murmur immediately following the first heart sound. The murmur could be heard with the stethoscope one cm. from the chest wall. At full inspiration this high pitched sound completely disappeared. Position did not affect the murmur; however, the musical systolic murmur completely disappeared for a few beats at full inspiration. There appeared to be an escape after a few beats and with post-inspiratory apnea the murmur gradually returned, becoming louder and louder with each beat (42). It is interesting and diagnostically important that respiration had converse effects in these two cases. In general the experience is that tricuspid murmurs are accentuated by inspiration, presumably because of increased venous return to the right side of the heart. On the other hand, venous return to the left side probably falls, as a rule, with inspiration and is increased with expiration. Mitral murmurs may show variations with respiration paralleling those in venous return to the left atrium.

A similar musical systolic murmur may be expected in cases of myxoma of the atrium.

Musical pulmonary systolic murmurs. Occasionally children and adolescents

with rheumatic heart disease demonstrate a musical systolic murmur in the pulmonary area. Its genesis is unclear. Fig. 26 presents an example of this phenomenon. The recording was made from an 18 year old white primigravida with a history of rheumatic fever. Since the musicality was evident at both the pulmonary area and the apex its exact origin is uncertain. Luisada (19) believes that murmurs of this type cannot be considered innocent in all instances.

Aberrant tendon ("moderator band") of the ventricle. The term "moderator band" was first introduced (16) because of a misconception of the function of these structures; that they prevent over-distention of the ventricle. This congenital anomaly, the analog, in a fluid system, of the Aeolian harp, has been observed to produce loud musical precordial murmurs under certain conditions. Normally they are silent. The patients often at earlier dates have had examinations showing no murmur. Later they develop ventricular dilatation on some independent basis such as hypertension or coronary arteriosclerosis. This pulls the aberrant tendon sufficiently taut to result in a musical murmur as blood is ejected by it during systole. Figure 27 presents a diagrammatic repre-

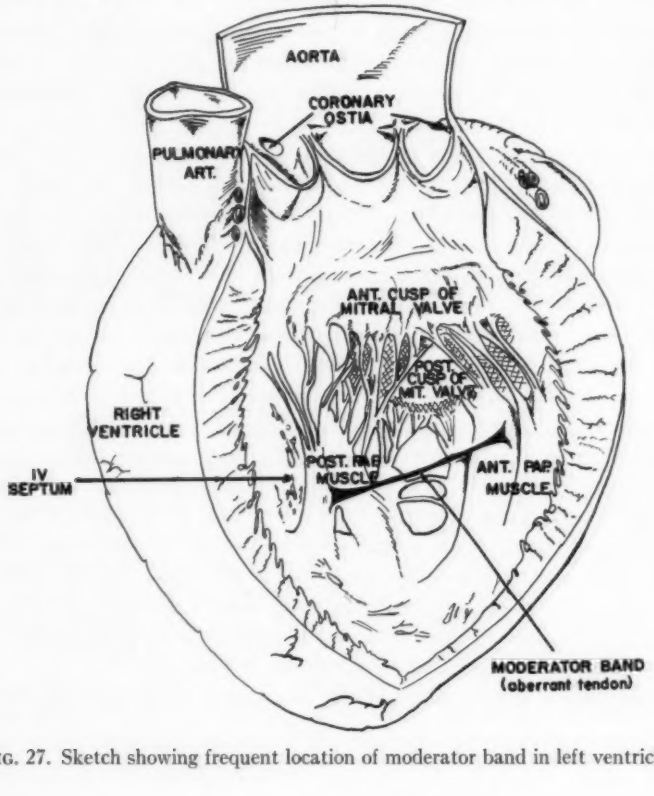

FIG. 27. Sketch showing frequent location of moderator band in left ventricle.

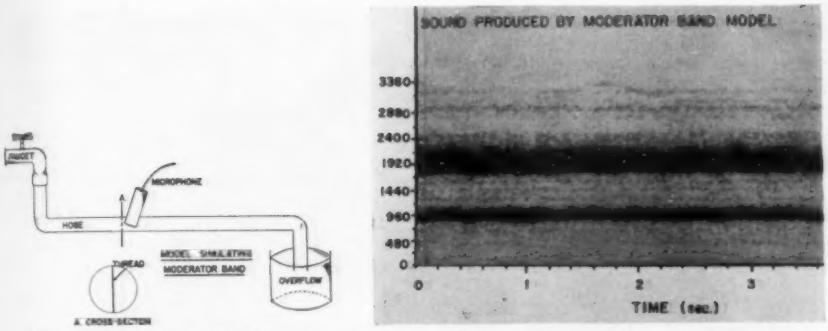

FIG. 28A. Model simulating the murmur-producing properties of aberrant tendons of the ventricle. B. Murmur recorded from the model diagrammed in A.

sentation of a frequent location of these violin-string-like bands, bridging the outflow tract of the left ventricle. The cases of Rolleston (17) and of Huchard (18), among others, displayed anatomical findings very much like those in the sketch.

In order to test the type of murmur which might be produced by an aberrant tendon of the ventricle, the model* sketched in Figure 28A was constructed. A rubber tube, one inch in diameter, was transfixed by a silk thread. When water ran through the tube and when the thread was taut a musical murmur with the appearance shown in Fig. 28B was produced. When the thread was lax no musical murmur was produced.

Two brief notes on patients with this type of musical systolic murmur, one in the literature and one in the files of this hospital, will serve to illustrate the usual clinical picture. In several cases Huchard (18) made the diagnosis *in vitam* and subsequently confirmed the impression at autopsy. In his first case, a 49 year old man seen in 1892, there was uremia, signs of severe arterial hypertension, cardiomegaly and heart failure. The conventional murmur of mitral regurgitation was heard at the apex and in the left axilla. More medially located, maximal in the area of the xiphoid but widely heard, especially to the right of sternum and up the course of the aorta was a purring or snoring systolic murmur ("une sorte de piaulement, de ronflement, de bruit de guimbarde"). Autopsy revealed a situation very much like that illustrated in Fig. 27.

In 1941 Dr. Arnold R. Rich presented at a clinical pathological conference (with Dr. Louis Hamman) a case similar to Huchard's: M. V. (J. H. H. 122170), a colored female patient who died at the age of 43 years, had been seen at this hospital twenty years previously at which time her heart sounds were normal. Four years before death she developed toxemia of pregnancy. At that time, too, the loud musical systolic murmur was not present. This pregnancy was

* We are indebted to Dr. A. R. Rich for suggesting this type of model.

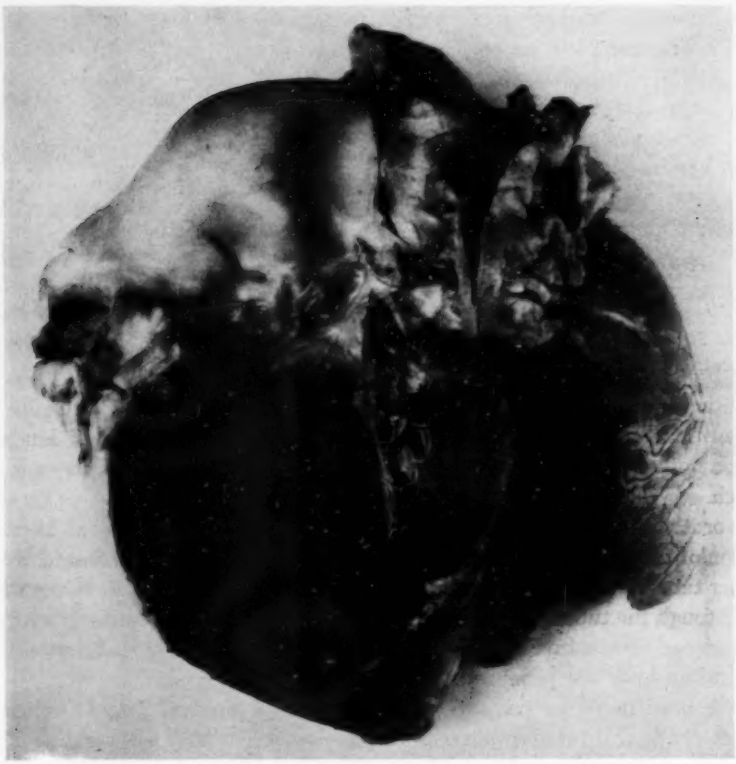

FIG. 29. Aberrant tendons in left ventricle. In life these were responsible for a highly musical systolic murmur.

followed by persistent hypertension and heart failure. It was with the development of heart failure that she was observed to have a loud harsh musical systolic murmur, accompanied by thrill, maximal in the left mid-precordial area. She was said to have been aware of the onset of a buzzing sensation. It was heard very widely; it was very loud over the back and could even be heard over the sacrum and head, but displayed no particular transmission to the vessels of the neck and the thrill was not transmitted to the neck. Later a diastolic murmur, thought to arise at the pulmonary valve, appeared at the left sternal border. At autopsy the heart weighted 560 gms. All chambers were greatly dilated, especially the left ventricle. The aortic valve was normal. The lower part of the cavity of the left ventricle was traversed by a net of aberrant tendons (see Fig. 29). The central portion was about 0.5 cm. long in its fixed state. At each end were attached two tendons, each about 1.2 cm. in length. It is believed that this anomaly was responsible for the musical murmur which

FIG. 30. Aberrant tricuspid chordae tendineae stretching across right ventricular aspect of high interventricular septal defect and probably responsible for the musical modality of the resulting murmur.

probably appeared only when ventricular dilatation occurred to pull the net taut and render it vibrant.

Ventricular septal defect with aberrant tricuspid chordae tendineae. The murmur of interventricular defect is occasionally rather musical. In some the basis for the musicality may be the anatomical set up in the patient illustrated in Fig. 30 (and in Fig. V 13 a–d of ref. 44). In high ventricular septal defect, the blood shunted from the left ventricle enters the right ventricle in the area traversed by the chordae tendineae of the septal leaflet of the tricuspid valve. Furthermore, not uncommonly, certain of these chordae are anomalous in that both their superior and their inferior attachments are to the corresponding margins of the defect. Such was the case in this patient in whom the aberrant chordae extended across the opening. In an earlier publication harmonics were demonstrated in the systolic murmur of IV septal defect (see Fig. 6A of ref. 2).

Musical murmurs with ventricular aneurysm. Recently Vakil (49) has written that in five of twenty cases of ventricular aneurysm, all presumably following myocardial infarction, a phenomenon with the following characteristics, was observed: "a fairly loud and long murmur, with a peculiar 'cooing', 'plaintive', or musical character, occupying the whole of systole and early part of diastole,

best heard at the site of the cardiac impulse, and not conducted in any particular direction." He refers to the description by Remlinger (50) in 1896 of a patient in whom the diagnosis of ventricular aneurysm was made in life mainly on the basis of a loud musical systolic and early diastolic murmur well localized midway between the xiphoid and left nipple and uninfluenced by the patient's phase of respiration or position, or by pressure on the stethoscope. He attributed the early diastolic component to the return of blood to the ventricle from the aneurysm at that time in the cardiac cycle.

We have not had an opportunity to observe this phenomenon. One would be suspicious that the mechanism of the murmur might be pericardial roughening or mitral regurgitation since both can produce systolic diastolic murmurs which may be musical. In all, then, three mechanisms for this phenomenon in patients who have had myocardial infarction can be imagined.

CONTINUOUS PERIPHERAL VASCULAR MURMURS OF MUSICAL QUALITY

The uterine souffle detected over the lower abdomen in pregnancy may be strikingly musical in quality. In such instances the spectral phonogram may, as was previously demonstrated (see Fig. 13 of ref. 2), display a striking resemblance to an arterial pulse pressure tracing. Only a fundamental was recorded and during the cardiac cycle the frequency level of the fundamental showed variations paralleling those of pressure at the site of origin of the murmur. The murmur has its origin in the dilated and tortuous uterine arteries which are conducting a much increased volume of blood to the pregnant uterus. Assuming substantially constant resistance throughout any one cardiac cycle, volume of flow is proportional to pressure. Velocity of flow in turn is proportional to volume of flow. Finally the frequency level of the fundamental is directly proportional to velocity. This chain of proportionalities (which indicates the basis for the resemblance of the spectrogram to an arterial pressure curve) can be represented by "$P \propto F \propto V \propto f$" where the symbols stand for pressure, volume of flow, velocity of flow, and frequency, respectively. In no case of musical uterine souffle have we recorded more than the fundamental.

The Cruveilhier-Baumgarten murmur: Other peripheral vascular murmurs, notably that with which the names of Cruveilhier and Baumgarten are associated, may be strikingly musical. The murmur in these cases is generated in the anastomotic communications between the portal and caval venous systems. On rare occasion these communications may be congenital and be primary to the hepatic atrophy present (31). More commonly the anastomoses are the result of the portal venous hypertension produced by hepatic cirrhosis. The murmur may resemble the buzzing of bees, the humming of a top, the sound of a spinning wheel or an Aeolian harp (35).

It is a continuous murmur. Accentuation of intensity and pitch with each heart beat is often but not invariably present. Pitch and intensity tend to

vary together with respiration and with the volume of peritoneal effusion. The murmur is usually attenuated in expiration and after abdominal paracentesis. The murmur can often be obliterated by light pressure in the epigastrium (32). In other instances a non-musical venous hum becomes musical with appropriate pressure by the pick-up unit of the stethoscope or recording microphone.

ANALOGIES TO MUSICAL INSTRUMENTS

The mechanisms of production of some of the musical murmurs have points of resemblance to those of certain musical instruments (30, 47). The retroverted aortic cusp suggests the reed of a musical instrument. The Aeolian harp is imitated by aberrant tendons of the ventricle and by interventricular septal defect with aberrant tricuspid chordae tendineae. In the case of some cardiopulmonary murmurs, the probable mechanism resembles that of the primitive pipe. In the case of pericardial musical sounds the mechanism may resemble that of the bowed string instruments, such as the violin.

SUMMARY AND CONCLUSIONS

A classification of musical murmurs has been proposed. Musicality is a function of the presence of harmonic pattern.

The clinical pictures (with particular reference to the musical murmur) associated with retroverted aortic cusp, ball-valve atrial tumor, aberrant tendon of the ventricle, and dissecting aneurysm of the ascending aorta with musical late diastolic murmur have been discussed briefly. A musical early diastolic murmur can have an extracardiac and prognostically benign basis.

The following hemodynamic and anatomical mechanisms in the genesis of musical murmurs are of particular interest:

1. It is possible to dissect the systolic murmur of aortic stenosis and the diastolic murmur of retroverted aortic cusp into musical elements related to the regular vibrations of an elastic structure and noisy components due to turbulence. Certain of these musical murmurs are the loudest known to medicine. Components of the same two general types may be present in the valve closure sounds.

2. In general, frequency and intensity in aortic murmurs, both systolic and diastolic, vary directly with aorto-ventricular pressure differential.

3. Selective transmission results in alteration in the timbre of the murmur of retroverted aortic cusp as heard at the apex. Resonant absorption apparently operates in changing the timbre of the same murmur as heard in the "aortic" area (which is, of course, removed from the site of the generator at the aortic ring).

4. The shape of the musical uterine souffle, which resembles an arterial pressure pulse curve, can be related to cyclical hemodynamic changes at the generator.

ACKNOWLEDGMENTS

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ABSTRACTS OF PAPERS PRESENTED BEFORE THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY IN ASSOCIATION WITH THE ALPHA OMEGA ALPHA FRATERNITY

May 9, 1955

SYSTOLIC CLICKS (SO-CALLED SYSTOLIC GALLOPS): A STUDY OF THEIR CLINICAL SIGNIFICANCE

JAMES A. REID* AND J. O'NEAL HUMPHRIES†

(Presented by Mr. Humphries)

The following classification of systolic clicks is proposed:

I. Those due to arterial abnormalities.
   a) Dilatation of the pulmonary artery, as in mitral stenosis, interatrial septal defect, and patent ductus arteriosus.
   b) Dilatation of the ascending aorta, as in atherosclerosis, hypertension and syphilitic aortitis.

II. Those arising by extracardiac mechanisms.
   a) Pleuropericardial adhesions.
   b) Plaques of calcification in the pericardium.
   c) Grating of xiphosternal, costochondral, or chondrosternal joints by ventricular contraction.
   d) Uncoiling and dilatation of auricular appendage with mitral regurgitation.
   e) Systolic expansion of ventricular aneurysm.
   f) Mediastinal emphysema.
   g) Left pneumothorax.

III. Atrial sound in systole due to low nodal pacemaker with retrograde conduction (ectopic atrial gallop).

Patients with systolic clicks were studied by means of spectral phonocardiography. The physical characteristics of systolic clicks, as demonstrated by the spectral phonocardiograms, are as follows:

1) Brief duration.
2) Tendency to "pure" frequency content.
3) Elevated frequency "bottom" as compared to valve closure sounds.

Systolic clicks of arterial origin, or the so-called "ejection vibrations", presumably result from the sudden tensing of the wall of the great vessel. These clicks are in early systole and are likely to be confused for splitting of the first heart sound. Pleuropericardial adhesions and grating of costochondral or chondrosternal junctions are the most frequent causes of systolic clicks. The grating sounds of the joints of the anterior thoracic cage have led to the misdiagnosis of pericarditis.

A motion picture of the fluoroscope image of the uncoiling and dilatation of an auricular appendage with each ventricular systole, as well as roentgen kymograms of the same phenomenon, was presented. This phenomenon appears to explain the systolic click in this patient with mitral regurgitation.

In general, these studies indicate that systolic clicks are of benign prognostic significance.

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The systolic click does not hold the same grave prognosis as does a diastolic gallop. For this reason, it is recommended that the term "systolic gallop" be abandoned.

Late systolic clicks may be confused with split second sound or may, with the normal second sound, create a combination simulating second sound plus opening mitral snap.

Circumscribed midsystolic murmurs introduced by a systolic click appear to be extracardiac in origin and hold the same prognosis as do systolic clicks without murmurs.

HYPOPHYSECTOMY AND DOMESTICATION IN THE NORWAY RAT

David E. Wood*†

The effect of domestication on the response of the Norway rat to hypophysectomy was studied. 71 of the wild form, trapped in city alleys and gutters, and 31 of the domesticated form, the common laboratory rat, were hypophysectomized and records made of their spontaneous running activity, body weight and food and water intake. They were given a modified McCollum diet. All rats had a postoperative decrease in water intake and atrophy of the target organs.

After hypophysectomy 44 per cent of the wild rats died after a variable length of time, whereas 100 per cent of the domesticated rats lived until they were killed 40 or more days postoperatively. The operation produced no obvious effect on the behavior of either wild or domesticated rats. After hypophysectomy the adrenals, pancreas and liver decreased more in the wild rat, and the thyroid and spleen more in the domesticated rat; the gonads, kidneys and thymus changed to the same degree in both types of rat. The greatest change occurred in the adrenals, which are much larger in intact wild rats. After operation this difference almost disappeared. The decrease in adrenal weight was the result of marked reduction in width of the zonae fasciculata and reticularis, a reduction which was much greater in the wild rat.

These results were discussed in relation to a relatively greater importance of the pituitary in the wild than in the domesticated rat.

AN ATTEMPT TO DEMONSTRATE "ERYTHROPOIETIN" IN DOGS‡

W. Paul Reagan§

Many investigators in recent years have attempted to demonstrate a specific plasma factor responsible for the erythropoiesis of anoxic and anemia stress. In reviewing this subject we realized that no evidence has yet been reported which demonstrates a true polycythemia, that is an expansion of total red cell mass, as a result of the administration of this proposed erythropoietic factor. In an attempt to study this problem we set up the following experiment.

We collected plasma from a random group of dogs received from the dog pound. The first sample collected from each of the dogs was saved as normal plasma. In each case the

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‡ This work was conducted in conjunction with Dr. Charles Sinn of the Department of Medicine and under the direction of Dr. C. Lockard Conley, Associate Professor of Medicine at The Johns Hopkins University School of Medicine. The facilities at the National Institutes of Health were made available through the courtesy of Dr. Paul Altland, Bethesda, Md.

§ Received a student research grant from the National Foundation of Poliomyelitis.

hematocrit was within normal limits. We then bled these dogs on successive days until their hematocrit had dropped to from 25 to 50 per cent of the original value. Plasma collections were then made which are denoted as anemic plasma. The reticulocyte count of these samples ranged from 5 to 18 per cent. Plasma denoted as anoxic plasma was collected from 7 healthy dogs subjected to an altitude of 25,000 feet 8 hours per day 5 days per week in the high altitude chamber of the National Institutes of Health. On the fifth day of each week, shortly after decompression, these dogs were bled to the extent that their hematocrits remained at normal levels instead of rising to values as high as 75 per cent, which normally result at this altitude. Reticulocyte counts on these specimens showed an increase of 0 to 4 per cent over the control levels. All plasma was frozen for storage.

We splenectomized 4 young dogs from 1 to 6 months before they were used. Their hematocrits became stabilized but their reticulocyte counts varied from 0 to 20 per cent. Dog 4 had to be transfused in order to achieve a stable hematocrit.

We infused the collected plasmas into the splenectomized dogs as described below. Just before the first infusion, total red cell mass was determined in each dog by the use of red cells tagged with radioactive chromium. Daily hematocrit and reticulocyte counts were performed, samples being drawn just before the day's infusion was to begin. At the end of the infusions total red cell mass was again determined.

Our results were as follows:

Dog 1—was infused with 11 per cent of his body weight of anemic plasma. An unexplained reticulocytosis of 20 per cent in the control specimen decreased with these infusions to a low of 8 per cent. The hematocrit decreased from 42 to 35 returning to control levels on the sixth day after the last infusion. The red cell mass increased by about 10 per cent.

Dog 2—was infused with 14 per cent of his body weight of anemic plasma. This infusion was followed by a decrease in reticulocytes from a control of 5 per cent to 0 in 500 cells. There was a drop in the hematocrit during the infusions. The red cell mass was decreased by about 11 per cent.

Dog 3—was infused with almost 30 per cent of her body weight of anoxic plasma.

There was a progressive rise of reticulocytes to a high of 24 per cent except for one low value on the eighth day of infusion. The hematocrit fell slightly with the infusions but rapidly returned to control values. The red cell mass, however, decreased by almost 20 per cent.

Dog 4— was infused first with 12 per cent of his body weight of normal plasma. This was followed by a slight drop in hematocrit without change in reticulocytes. There was a 15 per cent decrease in red cell mass. After a three day rest in which the hematocrit decreased by 2 per cent and the reticulocytes remained stable, he was infused with 11 per cent of his body weight of the anoxic plasma. This infusion was followed by a reticulocyte response to 18.9 per cent on the fourth day of infusion. The hematocrit dropped slightly during the infusions, but the red cell mass decreased by another 15 per cent.

On the fourth day after the last infusion the percentage of reticulocytes began to rise. On subsequent days the hematocrit fell rapidly and on the twelfth day after the last infusion the hematrocit was 12 and the reticulocytes were 56 per cent. It has subsequently been shown that this dog was infected with Bartonella canis, an organism known to produce a hemolytic anemia in the splenectomized dog.

IN CONCLUSION

We have attempted to study the effect of the infusion of normal, anemic and anoxic dog plasma into splenectomized dogs. The recipients were studied with regard to hematocrit, reticulocytes and determination of total red cell mass.

Our studies seem to indicate that:

1. Reticulocytosis is not an adequate index of erythropoiesis in the splenectomized dog. Our control specimens had reticulocyte counts varying from 0 to 20 per cent. An increased reticulocyte count did not correlate with any increase in red cell mass.

2. For whatever it may mean infusion of anoxic plasma seemed to be followed by a reticulocytosis which was not observed following the infusion of normal or anemic plasma.

3. The incidental observation of a severe hemolytic anemia secondary to infection with Bartonella canis points out the difficulties inherent in using splenectomized dogs as subjects for hematological research.

CONVERSION OF CHOLESTEROL TO CORTICOSTEROIDS IN ADRENAL HOMOGENATES

EDWARD REICH

A method of preparing cell-free homogenates of adrenal glands, capable of synthesizing corticosteroids in vitro, was described. The metabolic requirements and kinetic characteristics of the enzyme system were discussed. Corticosterone and 17-hydroxycorticosterone were identified as the major products accumulating. Two other, as yet unidentified steroids, were regularly produced by the extracts. By means of C^{14}-labelled compounds it was established that cholesterol, but not acetate, could function as a corticosteroid precursor in these extracts. ACTH did not affect any of the metabolic pathways investigated.

THE INFLUENCE OF HORMONAL FACTORS AND OF DIET UPON HEPATIC GLUCOSE-6-PHOSPHATASE ACTIVITY

ROBERT G. LANGDON AND DAVID R. WEAKLEY*

It is well known that hepatic utilization of glucose is impaired in alloxan diabetes. It has been suggested that the enzyme hexokinase is less active in the diabetic animal than in the normal, resulting in an impairment of the conversion of glucose to glucose-6-phosphate (1, 2). The presence in liver of a specific glucose-6-phosphatase responsible for contributing free glucose to the blood from the liver glycogen pool and from other precursors of glucose-6-phosphate has been demonstrated by Swanson (3) and de Duve and coworkers (4, 5). Since the net rate of formation of glucose-6-phosphate depends upon the relative activities of these two enzymes, it is apparent that an increased activity of hepatic glucose-6-phosphatase could cause a decreased net utilization of glucose by the diabetic liver, even in the presence of a normally functioning hexokinase reaction.

We have investigated the hepatic glucose-6-phosphatase activity in normal rats and in rats rendered diabetic by the administration of alloxan, and the results are given in Table I (6). Two enzyme preparations were used, one being a whole homogenate of rat liver cells, the other consisting only of rat liver microsomes. The enzyme preparations were incubated with the substrate, glucose-6-phosphate, at a pH of 6.5 for thirty minutes at a temperature of 30.5°C. Enzymatic activity was determined by measuring the amount of inorganic phosphate appearing in the assay tubes, which was proportional to enzymatic activity. It is apparent that the activity of the enzyme is greatly increased in the diabetic animals. It is also seen that the administration of insulin restores the enzymatic activity of the diabetic animals to near normal levels. The increased activity of the enzyme seems to be related rather specifically to the diabetic state since fasting and the administration to normal rats of

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TABLE I

Glucose-6-Phosphatase Activity in Normal and Diabetic Rat Liver

Experiment	No. Animals	Whole Homogenate[a]		Microsomes	
		SA[b]	TA[c]	SA[b]	TA[c]
		μ moles P		*μ moles P*	
Normal	16	5.1(±0.6)[d]	23.4(±3.2)	3.1(±0.4)	14.3(±2.0)
Diabetic	6	12.1(±1.1)	55.8(±7.6)	7.8(±1.1)	36.2(±8.6)
Insulin-treated[e] diabetic	4	5.5(±0.9)	34.1(±4.3)		

[a] The "whole homogenate" consists of the mitochondrial, microsomal, and soluble components of the cell.

[b] SA = μmoles of phosphorous liberated from glucose-6-phosphate per minute by the enzyme derived from one gram of rat liver.

[c] TA = (SA × total weight of liver × 100/body weight of animal).

[d] Values in parentheses represent the standard deviation.

[e] 200 units Protamine Zinc Insulin per kilogram of body weight administered subcutaneously 12 hours prior to sacrifice.

pituitary growth hormone, cortisone and adrenal cortical extract had little or no effect upon the enzyme.

It is not yet clear whether or not insulin directly affects the activity of this enzyme. However, the observed increase in activity could account for the decreased glucose utilization which has been repeatedly observed in diabetic liver.

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BIOELECTRIC PHENOMENA AS ETIOLOGICAL FACTORS IN INTRAVASCULAR THROMBOSIS: FURTHER STUDIES

Clarence S. Weldon

Whenever blood vessels are damaged platelets separate from the blood stream and adhere to the damaged vascular wall. The factors responsible for this phenomenon have never been explained.

Previously reported experiments[1] have shown that when the electrical potential gradient

[1] Weldon, C. S.: Bioelectric phenomena as etiologic factors in intravascular thrombosis. Bull. Johns Hopkins Hosp. 1954, **94:** 350.

is measured between the blood stream and a point on the external vascular wall there occurs a reversal of the polarity of this gradient following damage to the vessel. The external surface of the vessels becomes positive with respect to the blood stream. This finding suggested that vascular damage provides a reversed electric field in which platelets could by virtue of their electrical surface charge be attracted to the injury site.

Because such a theory depends on a knowledge of the electrical properties of blood platelet surfaces the following experiments were undertaken.

When charged particles are placed in an electric field the direction and speed of the particle is a direct reflection of the sign and magnitude of its surface charge so long as the strength of the field is constant. The technique of microelectrophoresis provides a method of measuring the speed of microscopic particles as they migrate in an electric field. Platelets were secured from fresh human blood by centrifugation techniques and suspended in citrated or heparinized plasma, in isotonic buffered solutions, or in isotonic buffered solution to which had been added varying constituents of human blood. Electrophoretic mobility rate determinations were then made on the suspended platelets.

The mobility rate value found for 17 samples of platelets suspended in autogenous citrated or heparinized plasma was 0.60 ± 0.04 μ/sec/v/cm. with migration towards the anode. When platelets were washed and resuspended in isotonic saline they continued to demonstrate a negatively charged surface but the mobility rate fell to the range of 0.51 ± 0.04 μ/sec/v/cm. This reduction of surface charge is thought to be due to the removal of plasma protein from the platelet surface.

It could readily be shown that the surface charge of platelets is influenced by the H^+ ion concentration of the surrounding medium and that if sufficient acid is introduced the platelets will be brought to an isoelectric point. Mobility rate determinations were made on platelets suspended in isotonic solutions buffered at various pH values. When the mobility rate values were plotted against the pH of the suspending medium a curve resulted which has a shape strikingly like that of a protein titration curve with the isoelectric zone for platelets being $pH = 4.01 \pm 0.10$. This value remained constant with time and is thought to represent a physical constant for the platelet surface. Curves were then constructed in a similar way from mobility rate determinations made on platelets suspended in isotonic buffered solutions to which had been added human plasma protein fractions[2] (Cohn fractions I, II, III, IV and V). All of the resulting curves showed a shift of the platelet isoelectric point to a more alkaline range. Since the zone of isoelectricity for all these proteins is more alkaline than the zone of isoelectricity for washed platelets, it is thought that the demonstrated shift is due to the absorption of protein on the platelet surface.

These experiments have shown that (1) human blood platelets are strongly negatively charged within the physiological pH ranges of blood, (2) there is a characteristic pH zone in which human platelets are isoelectric, (3) the surface of platelets is reactive and capable of some sort of union with plasma proteins.

It seems probable that, when vascular damage produces an electrical potential gradient with the negative stream being toward the point of injury, platelets would by virtue of their strong negative charge be attracted towards the injury site. As regards spontaneous thrombosis independent of demonstrable vascular damage, no constituent of human blood has thus far been found which will cause a reversal of electric charge on the surface of blood platelets within the physiologic pH ranges of blood.

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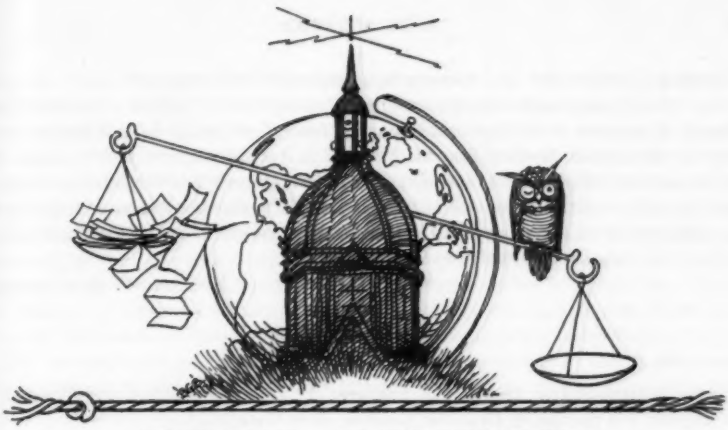
[2] Kindly supplied through the facilities of the American Red Cross.



BOOK REVIEWS

The Casualty Department. By T. G. LOWDEN. 278 pp., $7.50. E. & S. Livingstone Ltd., Edinburgh and London. The Williams & Wilkins Co. Baltimore, Md.

This is an unusual and interesting book. The reviewer intended skipping through it lightly but found his interest held to the point of reading it word for word.

The first third of the text deals with the use and abuse of antibiotics in the treatment of such infections as are handled in the outpatient casualty department, our accident room. Mr. Lowden points out that antibiotics given systemically cannot enter into pus cavities because of the impervious membrane formed by the necrotic tissues lining the inside of the cavity, but that if the lining is gently removed at the time of the incision and evacuation of pus, the antibiotic will be most effective in sterilizing the cavity. Accordingly, he advocates and practices the incision of abscesses (even perianal), evacuating the pus and gently curetting the lining of the cavity under a high penicillin blood level. After the pus is evacuated the abscess is closed by primary suture and the antibiotic continued. Mr. Lowden states that this has been proven to be a more rational and efficient method of treating these lesions than the much more commonly used incision and drainage. Individual case reports are given for illustrations.

The middle third of the book is devoted to the common non-infected conditions that are seen in the outpatient department, with emphasis on their diagnosis and treatment rather than on their etiology and detailed clinical findings. There are many excellent practical suggestions about handling sprains, superficial wounds of different parts of the body, cut tendons and nerves, skin defects, minor burns, sebaceous cysts and lipomas, ingrown toenails etc.

The last third of the book describes the organization of a casualty department (accident room), its financial arrangements including the certificates to be made out, the legal responsibilities of the Casualty Department (accident room) surgeon and his legal protection in England. This part of the text applies specifically to the present socialized medicine system in Great Britain and is of interest to the American chiefly as a glimpse of how that system works. It also defines clearly the fundamental responsibilities of an accident room surgeon and the precautions he should take in any country. This part of the text also contains a chapter headed "Disposal" which indicates which cases should be admitted to the hospital for observation, gives a routine for observing doubtful head injuries, provides advice about specialty cases (Eye, ear, fractures etc.), and mentions sequelae such as causalgia, etc.

The book is well written in a conversational style and well illustrated.

It is a difficult book to classify. It contains the elements of a textbook of minor surgery, a manual of accident room organization, and a manual of medico-legal-financial facts as related to the English Medical Practice Act, but is not encyclopedic in any of the three fields. It selects for the accident room surgeon the essential points of the three texts that are applicable to his work. For the American it is an interesting supplement to a textbook of minor surgery and contains many practical points gleaned from an obviously large personal experience that are not recorded elsewhere.

RICHARD T. SHACKELFORD

Potassium Metabolism in Health and Disease. By HOWARD HOLLEY and WARNER W. CARLSON. 131 pp., $4.50. Grune & Stratton, New York, N. Y.

Prior to the development of flame photometry, which made quantitative analysis of potassium in biological fluid a simple task, there was only a small clinical literature on the subject of potassium in disease. There was, however, a rich background of experimental observations and the essential facts were established that potassium is the most abundant intracellular cation and that it has profound effects upon excitable tissue—nerve, heart, skeletal and smooth muscle. This is not to imply that all the answers were written, for flame photometry and awareness that distortions of potassium concentration could be disastrous in patients gave impetus to more detailed study of the role of potassium and to factors which affected its distribution and excretion. The literature is now enormous and having gone through the phase of amorphous eruption it is showing signs of form. While there is still much to be learned, the accumulated observations are probably ripe for agonizing reappraisal.

The aim of the authors of this monograph was to write a manual for the busy practitioner. Their discussion of the role of potassium in health and in disease is informative in that it recites in readable brevity many observations which have been committed to print. The usefulness of this information, however, is limited by the unfortunate absence of bibliographic references.

But the responsibility of the monographer transcends collection. His duty is selection based on his own comprehension of the good and the bad experiment, the relevant and the irrelevant observation. It is this critical selectivity which is missed in this monograph, and in consequence, although no despot can proclaim absolute doctrine here, many thoughtful students of potassium metabolism will question the relevancy, importance and interpretibility of much of the material dealing with the more fundamental aspects of the problem. It is not easy to see, for example, how data from the role of potassium in isolated enzyme systems sheds light on clinical manifestations of disorders of potassium metabolism. On the other hand, the clinical effects of distortions of potassium content and concentrations are reflections of disturbed excitable tissue, nerve and muscle, and these disturbances can be interpreted in terms of altered excitability, a simple approach which, though not necessarily correct, serves to unite experimental and clinical observations.

The strong points of the monograph lie in adequate descriptions of the clinical features of distorted potassium metabolism and in a sound discussion of their management.

K. L. ZIERLER

Porphyrins. Their Biological and Chemical Importance. By A. VANNOTTI. Translated by C. RIMINGTON. 273 pp., 50s. Hilger & Watts, Ltd., London, England.

Professor Vannotti of the University of Lausanne has written a new monograph of limited size (224 pages) comprehensively reviewing the role of porphyrins in disease and in nature. Translated into English by Professor Rimington the material is based on the author's extensive experience as head of the University Polyclinic at Lausanne. The author published an earlier book on this subject in 1937; the present publication is not a mere revision of the older monograph but an entirely new book. It appears to be quite up to date.

The first chapter concerns the physical-chemical characteristics of porphyrins. This is a useful chapter for reference because it includes all of the structural modifications of the porphyrins, their natural series, certain recent developments in the biosynthesis of porphyrins, and the information derived from chromatographic procedures. The second chapter concerns methods of extraction and quantitative determination of porphyrins and again is useful as a reference chapter in this increasingly important field. In a third chapter the author takes up porphyrins in nature and tells in an interesting way the important part that porphyrins play in biological life. This might well be done in a more imaginative way with an eye to the possible relationships in comparative biology.

The fourth chapter concerns physiological metabolism of porphyrins in man and takes up elimination of porphyrins, porphyrin levels in the blood, and normal metabolism of porphyrins. It is pointed out that there are two porphyrin isomers in the normal human body, I and III. Their origin is not yet understood but recent studies and pathological mechanisms have helped to elucidate this problem. The interesting allied question of the mechanism of breakdown of hemoglobin is discussed and some of the original work bearing on this question is brought out. In the fifth chapter, the author discusses changes in porphyrin metabolism in human pathology and takes up porphyrins in their relationship to various systemic diseases. Some of the interesting statements that are made are:

1) According to Boas, a sure sign of the presence of hemorrhage in the digestive tract is the presence of porphyrin in the feces of a patient on a hemin-free diet.

2) The excessive porphyrin production in sprue is related to an actual increase in intestinal production of porphyrin, to faulty intestinal absorption, to osteoporosis and the inability of bone to deposit porphyrin, and lastly, to the presence of a pernicious anemia-like condition in sprue which is known to be accompanied by excessive porphyrin production as the result of pathological erythropoiesis.

3) In human pathology we frequently find an increased elimination of porphyrin in hepatic diseases and Vannotti has found the increase in porphyrin elimination to be an extremely sensitive indication of hepatic function when the patient is on a diet free from porphyrin precursors. Another method of testing for hepatic function is to administer coproporphyrin by mouth and measure the increase in excretion in feces and urine in cases of decreased liver function.

4) Another form of hepatic lesion which may be accompanied by increase in porphyrin elimination is hepatic stasis resulting from cardiac deficiency, the author states. Elimination of the pigment is generally proportional to the degree of hepatic stasis.

5) In pernicious anemia there is a porphyrinuria independent of porphyrin production in the digestive tract, closely related to the erythropoietic function of the bone marrow. This porphyrin production undergoes a rapid decrease coincident with reticulocyte crises brought about by liver extracts and folic acid. The author notes that an exaggerated porphyrinuria is not, however, a constant phenomenon in pernicious anemia and many cases show only slight increases in porphyrin in the urine.

6) The author states that we find cutaneous lesions only in cases where the body's porphyrin concentration is markedly elevated or where the porphyrin concerned is particularly photoactive, as in porphyria. The author then spends 24 pages discussing the many miscellaneous causes of increased coproporphyrin in urine.

The sixth chapter concerns the biological action of porphyrin and discusses the interesting phenomena of photo-sensitization, the action of porphyrins on the circulatory system, on the intestinal tract, and miscellaneous effects of porphyrins. The seventh chapter consists of 55 pages on the subject of porphyria; by case reports and a thorough discussion it gives a useful and comprehensive picture of this disease. The last chapter concerns treatment of porphyrin diseases and while it contributes little of specific value, it does give a useful discussion of the problems that are present.

The book is not long, can be read with ease due to a happy format, and is well annotated with references. It is a useful book on a relatively obscure subject and should be recognized as an excellent source for information on this problem. Specific errors were not noted and it is felt that the book is quite accurate. It is quite conservatively written and does not offer too much speculation. On the other hand, I think that the statements made are sometimes a little on the arbitrary side in view of the paucity of knowledge on this subject. The author is to be congratulated on fulfilling a useful need in the field of medicine.

FREDERICK W. BARNES, JR.

Clinical Bacteriology. By E. JOAN STOKES. 288 pp., $5.00. The Williams and Wilkins Co., Baltimore, Md.

This is a splendid book, primarily because Dr. Stokes has chosen to emphasize the *similarities* between "academic" bacteriology and "clinical" bacteriology rather than the *differences*. The task of the routine hospital laboratory is depicted as an exciting challenge and the entire text is in accord with the statement made by Dr. A. A. Miles in the foreword: "Clinical bacteriology is an exploratory art that demands flexibility of mind and technique, and the latest methods are less important to the (would-be) practitioner than a set of uniformly good procedures with which to explore the common and not-too-rare infections of man, and with which he stands a reasonable chance of discovering new ones."

This is not a "cook-book" type of laboratory manual that will be quickly out-dated. Rather, it is a careful exposition of the basic principles of microbiology and immunology underlying the practice of diagnostic bacteriology and also a storehouse of practical advice. With certain details, the reviewer would differ (such as the advice that blood cultures should be taken only by laboratory workers). This and several similar points seem more dependent upon the geography and personnel of a given hospital than upon some basic principle. A particularly valuable chapter concerns the author's extensive investigations of wound infection during the war and outlines a practical scheme of investigation for sources of contamination in hospital infections. This book should be available in all bacteriology laboratories and will be a valuable addition to the library of any clinician who has occasion to call upon such a laboratory for diagnostic aid.

IVAN L. BENNETT, JR.

Man: Mind Or Matter? By CHARLES MAYER. Translated and with a preface by HAROLD A. LARRABEE. 168 pp., $2.50. The Beacon Press, Boston, Mass.

This is a well written and clearly translated book that will interest those who have a philosophic turn and a curiosity about things outside of their field, for it hardly belongs to any one field. The author has a number of books to his credit in French on physics, chemistry and industry. This book is written in an easy conversational tone. Both the author and the

translator prepared themselves and the reader for disappointment, for they make it clear that they appeal only to the elite intelligentsia. "Dr. Mayer" states the translator, "is not for immature minds, and . . . may even be harmful to those who are not ready for it." "This book is an attempt to set forth a renovated and rejuvenated philosophy of rationalistic materialism." "It is, rather, much closer to the point of view of those Epicureans of antiquity who found their greatest happiness in conversation with their friends in an atmosphere of benevolent optimism." says the author. Hence, as we proceed to read and understand we gradually feel ourselves initiated into the fraternity of the elite and mature to whom Mayer and Larrabee make their appeal in their somewhat aloof endeavor to destroy hypocricy, muddled thinking and dogma.

Mayer discusses a number of current and interesting topics, e.g., chance and determinism, creation, evolution, mind and consciousness, free will, Marxism and ethics, and for each comes up with either a penetrating criticism or a solution. Some of these solutions seem too simple to be entirely adequate. For example, regarding free will, "what one group calls freedom and the other calls necessity is merely a matter of definition".

In the short chapter (ten pages) "Critique of Marxist Materialism", an excellent summary and evaluation is given of both Marxism and of Stalin's four points apropos of dialectic materialism. Stalin's first point, "that Nature is a uniform and coherent whole," would almost pass for a statement of holism by Smuts and some current would-be philosopher-psychiatrists. To this Mayer aptly retorts, "It is a good thing to picture things as a whole, but only after they have been understood in detail." Stalin's second point, that Marxist dialectic looks upon Nature as "a state of movement and perpetual change" is also almost a paraphrase of the principle of "dynamic psychiatry" so fashionable among current psychiatrists [I put on my shield and buckler to parry the blows that the "dynamic psychiatrists" will hurl against me if any read this]. Mayer refutes this: "In order to teach mechanics one begins by studying statics and dynamics before going on to kinematics." The fourth point, the Marxist dialectic against metaphysics, "not as a cyclical movement . . . but an evolution from the simple to the complex," is nullified by the observation that the principle of phase and evolution and contradiction (dialectics) reduced to its proper station is not a discovery of Marx. Mayer's real objection to Marxism is that it submerges the individual for the group—an ever widening pitfall confronting modern cultures. This chapter alone is worth the price of the book. It not only delineates and disposes of Marxist dogma, but serves as a warning to all those Pharisees who enthrone themselves on the seat of authority and isolate themselves within the pale of fine words and bombastic clichés. This is the lesson which the physician who would be a scientist may learn from this book.

When Mayer essays to solve all the mysteries of cosmic and biologic creation, of evolution, of motivation, I feel that he is on shakier ground. Some of his explanations even border on the thing he wants to defeat (mysticism). For example on page 33 he reveals the mechanism of plant perspiration not as a useful function to preserve the life of the plant, but "because the plant's cells hold water to the extent necessary for them to achieve the maximum feeling of well-being" yielding them a sensual satisfaction. Pleasure and pain are invoked as prime movers of living organisms whether plant or animal. This old Hedonistic principle has become not only outmoded, but immediately raises the question to this reviewer: how do we know what gives the plant or for that matter sometimes even the human being pleasure? to which the sole reply is, as I see it, By what they do. This circular reasoning gets us nowhere.

I am somewhat amazed that Mayer does not shrink from giving a solution to all the great mysteries that philosophers have pondered through the ages, such as creation, the nature of God, the beginning of life. However it seems to me a healthier approach to be clear about what he thinks than to hide behind a confusion of words and phrases.

To all those who have a curiosity about the big secrets of life and who revere honest and direct thinking, this book will provide interesting reading.

W. HORSLEY GANTT

Multiple Sclerosis. By DOUGLAS MCALPINE, NIGEL D. COMPSTON and CHARLES E. LUNSDEN. 304 pp., $7.00. E. & S. Livingstone Ltd., London, England. Distributed by The Williams & Wilkins Co., Baltimore, Md.

This able British survey of the unsolved problem of multiple sclerosis presents in concise and readable form the progress that has been made so far in the clinical and pathological understanding of this disabling disease. Beginning with an historical survey, it deals with questions such as geographical distribution, clinical manifestations, diagnostic criteria, and the various theories regarding etiology and treatment. The pathology of the disease is discussed in considerable detail, and its relationship to other demyelinating diseases. Statistical study of a series of more than a thousand cases is a feature of the clinical discussion.

The question of etiology is discussed in an interesting and thorough manner. Of the many etiological theories which have been advanced to explain multiple sclerosis, the authors are particularly impressed with the possibility of an allergic factor, and also with the possibility of an oligodendroglial dysfunction interfering with myelin synthesis, with these processes being possibly inter-related. However, they are careful to emphasize the incompleteness of our present understanding of the pathogenesis of this difficult disease, and the resulting problem of treatment.

GEORGE G. MERRILL

Antisera, Toxoids, Vaccines and Tuberculins in Prophylaxis and Treatment, 3rd edition. By H. J. PARISH. 227 pp., $5.00. Published for The Wellcome Foundation Ltd. by The Williams and Wilkins Co., Baltimore, Md.

This is the third edition of a useful book. Dr. Parish describes briefly the antisera, toxoids, vaccines and similar materials now available for therapeutic, preventive and diagnostic use. Methods of commercial preparation are described briefly and enough of the theoretical basis for the use of each agent is included to make the situation clear. There are no extravagant claims for any one preparation. Although the usage, methods, and standards referred to by Dr. Parish are primarily British, variations likely to occur in the United States are carefully mentioned. The book can be recommended to all who have occasion to use vaccines and antisera, particularly practicing pediatricians and internists. In addition, it is a ready source of information that is obtained with difficulty or not at all from larger works in the general field of microbiology or immunology.

IVAN L. BENNETT, JR.

BOOKS RECEIVED FOR REVIEW

Annual Review of Medicine, Vol. VI. Edited by DAVID A. RYTAND. 459 pp., $7.00. Annual Reviews, Inc., Stanford, California.

An Atlas of Musculoskeletal Exposures. By H. F. MOSELEY. 235 pp., $22.50. J. B. Lippincott Co., Philadelphia, Pa.

The Behavior of Pulmonary Tuberculous Lesions. A Pathological Study. By E. M. MEDLAR. 244 pp. Published by The American Review of Tuberculosis and Pulmonary Diseases.

Benjamin Franklin. Some Account of the Pennsylvania Hospital. Printed in Facsimile with an Introduction by I. BERNARD COHEN. 40 pp., $3.25. The Johns Hopkins Press, Baltimore, Md.

Bickham-Callander Surgery of the Alimentary Tract, Vols. I, II and III. By RICHARD T.

SHACKELFORD and assisted by HAMMOND J. DUGAN. 2575 pp., $60.00 per set. W. B. Saunders Co., Philadelphia, Pa.

Breast Cancer and Its Diagnosis and Treatment. By EDWARD F. LEWISON. 478 pp., $15.00. The Williams & Wilkins Co., Baltimore, Md.

The Effect of Sugar Supplements on Dental Caries in Children. Medical Research Council Special Report Series No. 288. By J. D. KING, MAY MELLANBY, H. H. STONES and H. N. GREEN. 55 pp., 4s. net. Her Majesty's Stationery Office, London, England.

Electrochemistry in Biology and Medicine. Edited by THEODORE SHEDLEVSKY. Sponsored by The Electrochemical Society, Inc., New York, N. Y. 369 pp., $10.50. John Wiley & Sons, New York, N. Y.

Erlebtes aus der Thorax-Chirurgie. By RUDOLF NISSEN. 64 pp., $3.40. Georg Thieme Verlag, Stuttgart, Germany. Intercontinental Medical Book Corp., New York, N. Y.

Experiencing the Patient's Day. A Manual for Psychiatric Hospital Personnel. By ROBERT W. HYDE. 214 pp., $2.20. G. P. Putnam's Sons, New York, N. Y.

Grundfragen der Neurosenlehre. By J. H. SCHULTZ. 215 pp., $5.70. Georg Thieme Verlag, Stuttgart, Germany. Intercontinental Medical Book Corp., New York, N. Y.

Krieslaufregulation. Eine Physiologische, pathophysiologische und klinische studie. By H. REINDELL, E. SCHILDGE, H. KLEPZIG and H. W. KIRCHHOFF. Foreword by Ludwig Heilmeyer. 315 pp., $9.40. Georg Thieme Verlag, Stuttgart, Germany. Intercontinental Medical Book Corp., New York, N. Y.

Living Bone in Health and Disease. By IRVIN STEIN, RAYMOND O. STEIN and MARTIN L. BELLER. 510 pp., $15.00. J. B. Lippincott Co., Philadelphia, Pa.

The Mayo Clinic, 2nd edition. By LUCY WILDER. 70 pp., $3.75. Charles C Thomas, Springfield, Illinois.

Neuropharmacology. Transactions of the First Conference May 26, 27 and 28, 1954. Edited by HAROLD A. ABRAMSON. 210 pp., $4.25. The Josiah Macy, Jr. Foundation, New York, N. Y.

Obstetrics, 11th edition. By J. P. GREENHILL. 1088 pp., $14.00. W. B. Saunders Co., Philadelphia, Pa.

Physiology and Anatomy, 7th edition. By ESTHER M. GREISHEIMER. 868 pp., $5.00. J. B. Lippincott Co., Philadelphia, Pa.

Practical Medical Mycology. (American Lecture Series). By EDMUND L. KEENEY. 145 pp., $4.50 and $3.75. Charles C Thomas, Springfield, Illinois.

Psychische Hygiene, Vol. IV. By ERNST BREZINA and ERWIN STRANSKY. 282 pp., $8.25. Wilhelm Maudrich, Vienna, Austria. Intercontinental Medical Book Corp., New York, N. Y.

Psychology in Nursing. By WENDELL W. CRUZE with a foreword by LUCILE PETRY. 494 pp., $5.50. McGraw-Hill Book Co., New York, N. Y.

Sexual Hygiene and Pathology. A Manual for the Physician. By JOHN F. OLIVEN. 481 pp., $10.00. J. B. Lippincott Co., Philadelphia, Pa.

Should the Patient Know the Truth? A Response of Physicians, Nurses, Clergymen, Lawyers. Edited by SAMUEL STANDARD and HELMUTH NATHAN. 160 pp., $3.00, Hard Cover, $2.00, Soft Cover. Springer Publishing Co., New York, N. Y.

Some Physiological Aspects and Consequences of Parasitism. Edited by WILLIAM H. COLE. 90 pp., $2.00. Rutgers University Press, New Brunswick, N. J.

Tea. A Symposium on the Pharmacology and the Physiologic and Psychologic Effects of Tea. Presented at a conference at the New York Academy of Sciences May 16, 1955. Edited by HENRY J. KLAUNBERG. 64 pp., $1.00. The Biological Sciences Foundation, Washington, D. C.

Vitamins in Theory and Pracitce, 4th edition. By L. J. HARRIS. 366 pp., $6.50. Cambridge University Press, New York, N. Y.